Diagnostic and Prognostic Value of History-taking and Physical Examination in Undifferentiated Peripheral Inflammatory Arthritis: A Systematic Review

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ABSTRACT. ***Objective.*** To review the diagnostic and prognostic value of history/physical examination among patients with undifferentiated peripheral inflammatory arthritis (UPIA).

Methods. We conducted a systematic review evaluating the association between history/physical examination features and a diagnostic or prognostic outcome.

Results. Nineteen publications were included. Advanced age, female sex, and morning stiffness were predictive of a diagnosis of rheumatoid arthritis (RA) from UPIA. A higher number of tender and swollen joints, small/large joint involvement in the upper/lower extremities, and symmetrical involvement were associated with progression to RA. Similar features were associated with persistent disease and erosions, while disability at baseline and extraarticular features were predictive of future disability.

Conclusion. History/physical examination features are heterogeneously reported. Several features predict progression from UPIA to RA or a poor prognosis. Continued measurements in the UPIA population are needed to determine if these features are valid and reliable predictors of outcomes, especially as new definitions for RA and disease states emerge. (J Rheumatol 2011;38 Suppl 87:10–14; doi:10.3899/jrheum.101098)

Key Indexing Terms:
SYSTEMATIC LITERATURE REVIEW UNDIFFERENTIATED ARTHRITIS
HISTORY TAKING PHYSICAL EXAMINATION PROGNOSIS

Rheumatologists routinely encounter patients with new-onset synovitis. Even after careful investigations to rule out common causes of joint swelling, many will not meet criteria for a classifiable rheumatic condition. A determination of the course of patients presenting with undifferentiated peripheral inflammatory arthritis (UPIA) is difficult to predict. Adding to the uncertainty is the observation that up to half of patients with UPIA will spontaneously remit, making judgment about whether to initiate treatment with disease modifying antirheumatic drugs (DMARD) increasingly complex[1,2].

This article is part of the 3e (evidence, expertise, exchange) Initiative in Rheumatology. The 3e Initiative and the resulting 10 recommendations on how to investigate and follow up UPIA are described in detail in a recent publication[3]. The objective of this article was to systematically review the diagnostic and prognostic value of history-taking and physical examination among patients with UPIA.

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MATERIALS AND METHODS

Rephrasing the research question. The clinical question formulated by the experts was translated into epidemiological terms according to the PICO method[4] (Patients, Intervention/index test, Comparison, Outcome). Two separate searches were conducted for diagnostic and prognostic questions. Patients were defined as adults (≥ 18 years) with UPIA; Intervention was defined as elements obtained on history-taking or physical examination; there was no true "Comparator" for diagnostic studies, while normal history/physical examination served as Comparator for prognostic studies; Outcomes for diagnostic studies included development of any classifiable rheumatic condition; and Outcomes for prognostic studies were 5-fold: persistent disease, remission/self-limiting disease, erosive disease, disability, and quality of life. Any definition for these outcomes, as long as explicitly stated in the methods, was accepted. Likelihood ratios (LR) and odds ratios (OR) were anticipated measures of association.

Search strategy. We performed a literature search for articles in Medline (1950 to December Week 4, 2008) and Embase (1980 to December Week 4, 2008). The comprehensive search included terms "undifferentiated arthritis," "history," and "physical examination," combined with "diagnostic" and "prognostic" studies (For full search strategy see online Appendix 1 available from: www.3eupia.com). We searched reference lists and abstracts from meetings of the American College of Rheumatology (ACR) and the European League Against Rheumatism from 2007 to 2008 to identify additional studies.

Inclusion criteria. Titles and abstracts of references were screened by

authors (BK and EV), and articles not clearly addressing the topic of interest were excluded. Selected articles were reviewed and the following inclusion criteria applied: observational studies, adult patients with UPIA, and data on one or more of the prespecified outcome measures.

Data extraction and quality assessment. Data regarding the utility of history/physical examination features were independently extracted by 2 investigators (BK and EV) and discrepancies were resolved by discussion. In studies with a mixed population of subjects, data on the subgroup of UPIA patients were extracted. A determination was made regarding the degree to which features were useful based on strength of association and its statistical significance [commonly presented as OR with 95% confidence intervals (CI)]. Wherever possible, OR derived from multivariate analyses were selected.

The methodological quality of diagnostic studies was evaluated with the quality assessment of diagnostic accuracy studies (QUADAS) tool[5]. We also assessed features most relevant to control of bias in prognostic studies[6].

RESULTS

Included studies. The literature search identified 2914 references matching search criteria. After title and abstract screening, 53 articles were retrieved for full-article review, in addition to 2 abstracts. In total, 19 studies fulfilled inclusion criteria. A detailed flowchart with reasons for exclusion is given in online Appendix 2, available from: www.3eupia.com.

Study characteristics. Characteristics of included studies are displayed in online Appendix 3, available from: www.3eupia.com. Studies were heterogeneous with respect to cohort size and composition. Many studies came from the same center (e.g., Leiden early arthritis clinic) and were primarily based in Europe. The outcomes of interest were typically ascertained at or after one year of followup. In virtually all studies (N = 18, 95%), measures of association were estimated by multivariate techniques, adjusting for the combination of history and physical examination factors. The majority of studies met criteria for sufficient methodological quality.

Diagnostic utility of history and physical examination features. The studies assessed a variety of history and physical examination features. These features were used to determine if progression from UPIA to one of the following 4 diagnoses was likely: rheumatoid arthritis (RA), reactive arthritis, spondyloarthritis, and osteoarthritis. However, the included studies quantified only the strength of association between these features and an eventual diagnosis of RA.

Five studies quantified aspects of history. Older age, female sex, and longer or more severe morning stiffness were found to have diagnostic utility (Table 1).

Physical examination findings found to be useful to identify development of RA included a higher number of tender and swollen joints, joint symmetry, and involvement of small joints in the upper and lower extremities (Table 1). In total, 7 features on history and physical examination were associated with progression to RA (Table 2).

Prognostic utility of history and physical examination features. A range of features was evaluated among prognostic studies. Disease persistence, remission, and development of erosions were more commonly reported. Few studies measured disability, and none examined quality of life or work productivity. A summary of predictive features for these outcomes is provided in Table 2.

Disease persistence. One study demonstrated that symptom duration > 12 weeks (OR 1.11, 95% CI 1.03–2.10)[13] was associated with persistent disease, while another found that symptoms > 6 months was predictive (OR 5.49, 95% CI not provided)[14]. Morning stiffness > 1 hour was identified as important (OR 1.16, 95% CI 1.09–1.22[15]; OR 1.96, 95% CI not provided[14]). Green, *et al* showed that a higher number of swollen joints had prognostic value (OR 18.0, 95% CI 3.68–87.9)[13]. Similarly, small joint or wrist involvement was important (OR 1.95, 95% CI 1.11–3.41[8]; RR 3.04, 95% CI 1.77–5.22[16]) in 2 studies. The presence of metatarsophalangeal compression pain was also suggested to be of value (OR 1.65, 95% CI not provided).

Remission. Various remission definitions were used, including the ACR remission criteria or being DMARD-free without arthritis symptoms. No studies considered remission according to the Disease Activity Score or other composite measures.

Intuitively, many features that best predicted remission or self-limiting disease directly contrasted with those for disease persistence. Male sex (OR 3.9, 95% CI 1.7–8.7[1]), symptoms less than 12 weeks (OR 4.9, 95% CI 1.3–17.8[17]), and older age (OR 3.2, 95% CI 1.2–8.7[18]) were found to increase the chance of remission. Fewer tender joints (OR 3.8, 95% CI 1.2–12.5[1]) and the lack of hand involvement were also favorable signs for remission (OR 0.18, 95% CI 0.05–0.66[19]).

Erosive disease. Age > 50 years was the only historical feature found to significantly increase the risk of erosive disease (OR 4.01, 95% CI 1.80–8.94[20]; OR 1.05, 95% CI 1.01–1.09[21]). Predictive physical examination findings included synovitis in the upper and lower extremities (OR 2.54, 95% CI 1.06–6.10[22]) and involvement of the hands, specifically (OR 4.2, 95% CI 1.04–17.0[21]). The presence of ≥ 3 swollen joints and metatarsophalangeal compression pain also had prognostic value (OR 1.73; OR 3.78, 95% CI not provided[14]).

Disability. Similar to other outcomes, disability was predicted among subjects of advanced age (OR 3.46, 95% CI 1.70–6.76[23]), female sex (OR 4.24, 95% CI 1.36–13.25[24]), and those with longer symptom duration (OR 1.11, 95% CI 1.01–1.22[24]). A high score on Health Assessment Questionnaire at baseline was associated with future disability (OR 3.52, 95% CI 1.15–10.77[24]; OR 12.4, 95% CI 6.23–24.8[23]). Extraarticular features on physical examination were also uniquely predictive of disability (OR 3.16, 95% CI 1.22–8.20[23]).

DISCUSSION

Management of UPIA is an emerging field. Investigators have searched for predictors that will help guide therapy to

Table 1. History and physical examination features with diagnostic utility for progression of undifferentiated peripheral inflammatory arthritis to rheumatoid arthritis (RA).

	Studies, n	Author	OR (95% CI)	Comment/Interpretation
Historical feature				
Age	2	van der Helm-van Mil[7]	1.02 (1.01–1.04)	Reported as continuous
		Mjaavatten[8]	1.05 (1.02–1.08)	Reported as continuous
Gender	2	van der Helm-van Mil[7]	2.1 (1.30–3.60)	Female sex predictive of RA diagnosis
		Mjaavatten[8]	1.67 (0.71–3.92)	Female sex not predictive of RA diagnosis
Morning stiffness	2	van Gaalen[9]	2.9 (1.20–6.50)	VAS severity of AMS > 90 mm diagnostic of RA
		van der Helm-van Mil[7]	9.3 (3.0–28.7)	Duration of AMS > 1 h diagnostic of RA
Painful joints	1	Quinn[10]	1.06 (1.00–1.12)	Self-reported pain not associated with RA
Reproductive history	1	Hernandez-Avila[11]	RR 1.0 (0.7–1.3)	Previous OCP/HRT use not predictive of RA
Physical examination feature				
Tender joints, n	2	Alarcon[12]	0.63 (0.27–1.46)	No association between no. of tender joints and RA diagnosis
		van der Helm-van Mil[7]	3.3 (1.50–7.00)	> 10 joints diagnostic of RA
Swollen joints, n	3	Alarcon[12]	2.93 (1.06–8.10)	> 6 swollen joints predictive of progression to RA
		van der Helm-van Mil[7]	2.8 (1.1–7.6)	> 10 swollen joints predictive of progression to RA
		van Gaalen[9]	5.8 (2.4–13.6)	> 3 swollen joints associated with RA diagnosis
Joint distribution	3	Mjaavatten[8]	5.64 (2.06–15.5)	Small joint involvement diagnostic for RA
		van der Helm-van Mil[7]	3.5 (1.7–7.5)	Upper/lower involvement associated with RA
			1.8 (1.1–3.1)	Small joints in hands/feet associated with RA
		van Gaalen[9]	1.8 (0.7–4.5)	MCP/PIP/wrist involvement not associated with progression to RA
Symmetry	2	van der Helm-van Mil[7]	1.6 (1.0–2.8)	Symmetrical involvement not predictive of RA
		van Gaalen[9]	2.6 (1.1–6.0)	Symmetrical involvement associated with RA

AMS: morning stiffness; VAS: visual analog scale; OCP/HRT: oral contraceptive pill/hormonal replacement therapy; MCP: metacarpophalangeal; PIP: proximal interphalangeal; RR: relative risk.

Table 2. Summary of history and physical examination features found to have diagnostic and prognostic value in UPIA.

	Eventual RA Diagnosis	Persistent Disease	Remission	Erosive Disease	Disability
Historical feature					
Older age, yrs	+		+	+	+
Female	+		+ (male)		+
Longer symptom duration		+	+ (shorter duration)		+
Longer/more severe morning stiffness	+	+			
Higher disability at baseline					+
Physical examination feature					
Higher tender joint count	+		+ (fewer joints)		
Higher swollen joint count	+	+		+	
Joint distribution (small/large, upper/lower)	+	+	+ (lack of hand involvement)	+	
MTP compression pain		+		+	
Symmetrical joint involvement	+				
Presence of extraarticular features					+

MTP: metatarsophalangeal.

prevent under-treatment among those destined to have persistent synovitis, and over-treatment for those with transient symptoms[7].

Even the most highly sensitive and specific diagnostic tests are no substitute for a thorough history and physical examination. A careful evaluation provides a preliminary impression, and some findings may be associated with important outcomes. Our systematic review identified 5 history and 6 physical examination findings that can help predict not only progression from UPIA to RA but also future development of persistent or remitting disease, radiographic erosions, and disability.

Our review has limitations worth noting. Many studies emanated from single arthritis centers, and measurement of baseline variables may have been influenced by the specific geographic distribution of risk factors among study participants. Risk factors typically associated with poor outcome in arthritis, such as smoking or comorbidity, were rarely evaluated[25]. Some features (e.g., age, joint distribution) were diagnostic and predictive of several different outcomes, and our review does not provide guidance on which factors, if any, should be weighed or deemed more important over any other. Further, studies focused primarily on RA. Statistical analyses and reporting of strength of association between given features and eventual diagnosis were not reported for other common rheumatic conditions that may present as UPIA, such as crystalline arthropathy or spondyloarthropathy. Interestingly, features known to correlate well with seronegative arthritides (e.g., recent infection, enthesitis) were noted in some studies but not quantified in a meaningful way. In addition, the low number and heterogeneity of quantified features prevented pooling of data to create aggregate measures. Lastly, no study provided guidelines with regard to the frequency at which history/physical examination should be repeated in patients with UPIA. Thus, "expert opinion" and clinical judgment should continue to serve as an adjunct when interpreting results of these evidence-based recommendations.

The identified factors in Table 2 resemble the 1987 ACR criteria for RA[26]. These variables would be expected to predict RA over other diagnoses and may lead to circularity. However, it may be argued that they reflect what is routinely measured in practice. Most clinicians are concerned with whether peripheral synovitis represents early stages of RA because this has important implications for treatment and followup. This cost-effective strategy of surveillance is significant, as a high proportion of UPIA patients will progress to RA within 1 year[7,9].

In summary, our review has identified easily measured clinical variables that may estimate the course of patients with UPIA. Future studies should consider how history/physical examination findings in combination with laboratory and radiographic imaging will aid in the prediction of other rheumatic diagnoses and prognostic outcomes. In addition, it will be important to see how these history-taking and physical examination features perform with the newly proposed RA criteria and with changing definitions of disease states such as remission and sustained remission[27]. Systematic collection and reporting of these features and outcomes will allow greater comparability between emerging cohorts of UPIA.

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