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

BINDEE KURIYA, EDITH VILLENEUVE, and CLAIRE BOMBARDIER

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 REVIEWUNDIFFERENTIATED ARTHRITISHISTORY TAKINGPHYSICAL EXAMINATIONPROGNOSIS

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

From the Division of Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto, Canada; and Academic Unit of Musculoskeletal Disease, Leeds University, Leeds, United Kingdom.

Supported by an unrestricted educational grant from Abbott. Abbott had no role in the design, literature search, data collection, data analysis, data interpretation, or writing of this report. Dr. Bombardier holds a Pfizer Chair and Canada Research Chair in Knowledge Transfer for Musculoskeletal Care.

B. Kuriya, MD, FRCPC, MS, Rheumatology, Mount Sinai Hospital, University of Toronto; E. Villeneuve, MD, FRCPC, Academic Unit of Musculoskeletal Disease, Leeds University, Leeds, UK; C. Bombardier, MD, Division of Rheumatology and Department of Health Policy, Management, and Evaluation, University of Toronto, Division of Clinical Decision Making and Health Care, Toronto General Research Institute, University Health Network, Mount Sinai Hospital.

Address correspondence to Dr. B. Kuriya, 313 Tappan Street, #1, Brookline, MA 02445, USA. E-mail: bindee.kuriya@gmail.com the resulting 10 recommendations on how to investigate and follow up UPIA are described in detail in a recent publication³. The objective of this article was to systematically review the diagnostic and prognostic value of history-taking and physical examination among patients with UPIA.

MATERIALS AND METHODS

Rephrasing the research question. The clinical question formulated by the experts was translated into epidemiological terms according to the PICO method⁴ (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

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2011. All rights reserved.

The Journal of Rheumatology 2011; 38 Suppl 87; doi:10.3899/jrheum.101098

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) tool⁵. We also assessed features most relevant to control of bias in prognostic studies⁶.

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 1.09–1.22¹⁵; OR 1.96, 95% CI not provided¹⁴). 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 1.11–3.41⁸; RR 3.04, 95% CI 1.77–5.22¹⁶) 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 1.7–8.7¹), symptoms less than 12 weeks (OR 4.9, 95% CI 1.3–17.8¹⁷), and older age (OR 3.2, 95% CI 1.2–8.7¹⁸) were found to increase the chance of remission. Fewer tender joints (OR 3.8, 95% CI 1.2–12.5¹) and the lack of hand involvement were also favorable signs for remission (OR 0.18, 95% CI 0.05–0.66¹⁹).

Erosive disease. Age > 50 years was the only historical feature found to significantly increase the risk of erosive disease (OR 4.01, 95% CI 1.80–8.94²⁰; 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 1.06–6.10²²) and involvement of the hands, specifically (OR 4.2, 95% CI 1.04–17.0²¹). The presence of \geq 3 swollen joints and metatarsophalangeal compression pain also had prognostic value (OR 1.73; OR 3.78, 95% CI not provided¹⁴).

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 1.36–13.25²⁴), 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 1.15–10.77²⁴; 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 1.22–8.20²³).

DISCUSSION

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

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2011. All rights reserved.

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 featur	es				+

MTP: metatarsophalangeal.

prevent under-treatment among those destined to have persistent synovitis, and over-treatment for those with transient symptoms⁷.

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.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2011. All rights reserved.

The Journal of Rheumatology 2011; 38 Suppl 87; doi:10.3899/jrheum.101098

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 evaluated²⁵. 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 RA²⁶. 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 remission²⁷. Systematic collection and reporting of these features and outcomes will allow greater comparability between emerging cohorts of UPIA.

REFERENCES

 Harrison BJ, Symmons DP, Brennan P, Barrett EM, Silman AJ. Natural remission in inflammatory polyarthritis: issues of definition and prediction. Br J Rheumatol 1996;35:1096-100.

- Van Aken J, van Dongen H, le Cessie S, Allaart CF, Breedveld FC, Huizinga TW. Comparison of long-term outcome of patients with rheumatoid arthritis presenting with undifferentiated arthritis or with rheumatoid arthritis: an observational cohort study. Ann Rheum Dis 2006;65:20-5.
- 3. Machado P, Castrejon I, Katchamart W, Koevoets R, Kuriya B, Schoels M, et al. Multinational evidence-based recommendations on how to investigate and follow-up undifferentiated peripheral inflammatory arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3e Initiative. Ann Rheum Dis 2010 August 19. [Epub ahead of print]
- Sackett DL, Richardson WS, Rosenberg WM, Haynes RB. Evidence-based medicine: how to practice and teach EBM. London: Churchill Livingstone; 1997.
- Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003;10:25.
- Hayden JA, Cote PC, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 2006;144:427-37.
- van der Helm-van Mil AH, le Cessie S, van Dongen H, Breedveld FC, Toes RE, Huizinga TW. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. Arthritis Rheum 2007;56:433-40.
- Mjaavatten MD, Nygaard H, Haugen AJ, Sidenvall G, Helgetveit K, Kvien TK. Baseline predictors of persistent arthritis, DMARD start and rheumatoid arthritis diagnosis: one year follow-up of 395 patients with very early arthritis [abstract]. Arthritis Rheum 2008;58 Suppl:S474.
- van Gaalen FA, Linn-Rasker SP, van Venrooij WJ, de Jong BA, Breedveld FC, Verweij CL, et al. Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. Arthritis Rheum 2004;50:709-15.
- Quinn MA, Green MJ, Marzo-Ortega H, Proudman S, Karim Z, Wakefield RJ, et al. Prognostic factors in a large cohort of patients with early undifferentiated inflammatory arthritis after application of a structured management protocol. Arthritis Rheum 2003;48:3039-45.
- Hernandez-Avila M, Liang MH, Willett WC, Stampfer MJ, Colditz GA, Rosner B, et al. Exogenous sex hormones and the risk of rheumatoid arthritis. Arthritis Rheum 1990;33:947-53.
- 12. Alarcon GS, Willkens RF, Ward JR, Clegg DO, Morgan JG, Ma KN, et al. Early undifferentiated connective tissue disease. IV. Musculoskeletal manifestations in a large cohort of patients with undifferentiated connective tissue diseases compared with cohorts of patients with well-established connective tissue diseases: followup analyses in patients with unexplained polyarthritis and patients with rheumatoid arthritis at baseline. Arthritis Rheum 1996;39:403-14.
- Green M, Marzo-Ortega H, Wakefield RJ, Astin P, Proudman S, Conaghan PG, et al. Predictors of outcome in patients with oligoarthritis: results of a protocol of intra-articular corticosteroids to all clinically active joints. Arthritis Rheum 2001;44:1177-83.
- Visser H, le Cessie S, Vos K, Breedveld FC, Hazes JM. How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis. Arthritis Rheum 2002;46:357-65.
- El Miedany Y, Youssef S, Mehanna AN, El Gaafary M. Development of a scoring system for assessment of outcome of early undifferentiated inflammatory synovitis. Joint Bone Spine 2008;75:155-62.
- 16. Tunn EJ, Bacon PA. Differentiating persistent from self-limiting symmetrical synovitis in an early arthritis clinic. Br J Rheumatol

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2011. All rights reserved.

Kuriya, et al: History/physical examination in UPIA

1993;32:97-103.

- Green M, Marzo-Ortega H, McGonagle D, Wakefield R, Proudman S, Conaghan P, et al. Persistence of mild, early inflammatory arthritis: The importance of disease duration, rheumatoid factor, and the shared epitope. Arthritis Rheum 1999;42:2184-8.
- Stockman A, Tait BD, Wolfe R, Brand CA, Rowley MJ, Varney MD, et al. Clinical, laboratory and genetic markers associated with erosions and remission in patients with early inflammatory arthritis: a prospective cohort study. Rheumatol Int 2006;26:500-9.
- Schumacher JHR, Habre W, Meador R, Hsia EC. Predictive factors in early arthritis: long-term follow-up. Semin Arthritis Rheum 2004;33:264-72.
- Bukhari M, Lunt M, Barton A, Bunn D, Silman A, Symmons D. Increasing age at symptom onset is associated with worse radiological damage at presentation in patients with early inflammatory polyarthritis. Ann Rheum Dis 2007;66:389-93.
- Jansen LM, van Schaardenburg D, van der Horst-Bruinsma IE, Dijkmans BA. One year outcome of undifferentiated polyarthritis. Ann Rheum Dis 2002;61:700-3.
- van der Horst-Bruinsma IE, Speyer I, Visser H, Breedveld FC, Hazes JM. Diagnosis and course of early-onset arthritis: results of a special early arthritis clinic compared to routine patient care. Br J Rheumatol 1998;37:1084-8.

- Wiles NJ, Dunn G, Barrett EM, Harrison BJ, Silman AJ, Symmons DP. One-year followup variables predict disability 5 years after presentation with inflammatory polyarthritis with greater accuracy than at baseline. J Rheumatol 2000;27:2360-6.
- Glennas A, Kvien TK, Andrup O, Karstensen B, Munthe E. Recent onset arthritis in the elderly: a 5 year longitudinal observational study. J Rheumatol 2000;27:101-8.
- 25. Oliver JE, Silman AJ. What epidemiology has told us about risk factors and aetiopathogenesis in rheumatic diseases. Arthritis Res Ther 2009;11:223.
- Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:316-24.
- 27. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580-8.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2011. All rights reserved.