Detecting the Earliest Signs of Rheumatoid Arthritis: Symptoms and Examination

Tabitha N. Kung, MD, MPH, FRCPC[a], Vivian P. Bykerk, MD, FRCPC[b,*]

KEYWORDS

• Preclinical disease • Symptoms • Clinical features • Examination

KEY POINTS

- The understanding of signs and symptoms associated with the development of rheumatoid arthritis (RA) is emerging.
- No definitive screening tool or a tool solely incorporating signs and symptoms has yet been validated as having sufficient predictive ability for RA.
- Studies of individuals at risk for RA need to include symptoms and signs that are not necessarily derived from classification criteria to provide new insights and novel detection tools.
- Qualitative methods applied to cohorts of individuals at risk of developing arthritis are integral to identify and validate novel symptom complexes important in preclinical disease.

INTRODUCTION

The concept of preclinical disease has gained increasing attention over the past decade as researchers and providers aspired to prevent and cure chronic disease. In seropositive autoimmune diseases, autoantibodies have been identified well before the onset of disease or even symptoms not only in type 1 diabetes[1] and celiac disease,[2] but also in rheumatic diseases, including rheumatoid arthritis (RA), antiphospholipid syndrome, and systemic lupus erythematosis.[3] Of the rheumatic diseases, prediagnosis and preclinical RA clinics are becoming more prevalent because RA is the most common of the inflammatory arthritides, affecting approximately 1% of the general population. These clinics follow those individuals at risk for RA in whom

Disclosures: Postgraduate fellowships from UCB and Janssen Canada (T.N. Kung).
[a] Department of Medicine, Mount Sinai Hospital, University of Toronto, Toronto, Ontario M5T3L9, Canada; [b] Division of Rheumatology, Hospital for Special Surgery, Weill Cornell Medical College, New York, NY 10021, USA
* Corresponding author.
E-mail address: bykerkv@hss.edu

Rheum Dis Clin N Am 40 (2014) 669–683
http://dx.doi.org/10.1016/j.rdc.2014.07.009 rheumatic.theclinics.com
0889-857X/14/$ – see front matter

risk may include the presence of autoantibodies without symptoms, symptoms without signs of synovitis, a first-degree relative (FDR) with RA, and/or a propensity to RA based on belonging to a specific at-risk population (eg, first nations). These clinics are generally aimed at identifying predictors of developing arthritis. Moreover, as the importance of the preclinical phase of inflammatory arthritis has gained prominence, the terminology describing persons in this preclinical phase has evolved. In a recent publication, the European League Against Rheumatism (EULAR) propose that prospective studies should use the following terminology to describe individuals at risk of RA having genetic risk factors for RA, having environmental risk factors for RA, having systemic autoimmunity associated with RA, having symptoms without clinical arthritis, and having unclassified arthritis.[4] These recommendations further suggest that "pre-RA" should refer to the period of time or phase, assessed retrospectively, before RA can be classified. Studies examining the pre-RA phase usually compare patients who were recently classified as RA and those not classified as RA but followed over a similar period of time. These studies compare risk factors in each group. The term "individuals at risk" implies a longitudinal study design in which individuals with risk factors for RA are followed to determine the probability of, or time course to, developing classifiable RA given a set of risk factors. This article focuses on individuals at risk who have symptoms and/or one or more other risk factors for RA but who have not developed clinical arthritis it also looks at studies that examined patients in the pre-RA phase.

Despite an increased interest in the preclinical phases of RA, there are few studies designed to examine the symptoms in this period. This article therefore extrapolates findings about symptoms in the preclinical phase from existing studies and summarizes these from studies that included information about clinical symptoms. Included are studies examining (1) screening tools to detect RA, and (2) physical features examined in cohorts of people with undifferentiated arthritis to predict who developed classifiable RA or persistent arthritis. This article also highlights the signs and symptoms being captured prospectively among patients followed in cohort studies of people at risk for RA, including cohorts of people who screened positively for increased risk of RA (eg, FDRs of individuals with RA, or those who carry antibodies associated with RA, or have symptoms without clinical arthritis [eg, arthralgia without synovitis]). Underscoring the need to understand symptoms in the presynovitis phase, a study by van de Stadt and colleagues[5] identified that joint symptoms are important components of predicting future RA in autoantibody-positive individuals initially without arthritis.

SCREENING AND TRIAGE TOOLS

Screening tools have been developed to screen populations with varying degrees of risk to detect people with RA. These tools may identify people with musculoskeletal (MSK) symptoms, or may be used to help triage those with symptoms or signs to either general practitioner or rheumatologist care in an attempt to improve early identification of inflammatory arthritis and RA. Because MSK symptoms are common, these tools are designed to identify only those people with true inflammatory disease. A recent systematic review of strategies to promote early diagnosis identified available screening tools to increase detection of individuals with inflammatory arthritis.[6] The symptoms queried by these self-report tools included questions about the presence of joint pain, stiffness, swelling, symmetry, duration of disease, and functional limitation (**Tables 1** and **2**). Some tools (such as the Connective Screening Questionnaire [CSQ]) were less specific for RA and queried an extensive list of extra-articular features