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Symptoms in individuals at risk of rheumatoid arthritis

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A B S T R A C T

An increasing interest in treating individuals at risk of rheumatoid arthritis (RA) to prevent the development of this chronic condition has focussed attention on the identification of risk factors of this disease. Most patients who develop RA progress through a preceding symptomatic phase that may take the form of arthralgia, palindromic rheumatism or unclassified arthritis before a disease currently classifiable as RA is established. An understanding of symptoms that identify individuals as being at risk of RA is a critical issue. Constellations of relevant symptoms could (1) form the basis of public health campaigns to encourage rapid consultation, (2) inform primary health care providers regarding which patients to perform additional tests in or whom to refer to a rheumatologist and (3) be included in algorithms to predict RA development. In this review, we present qualitative and quantitative data summarising current understanding of the symptoms experienced by individuals at risk of RA.

Introduction

Patients may transition between clinical states before rheumatoid arthritis (RA) manifests. Genetic and environmental risk factors predate the development of autoimmunity; in seropositive patients, the development of autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), can be present for up to a decade before symptoms emerge [1–3].

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Individuals at risk of RA may progress to develop symptoms but without clinical arthritis (a phase that has also been termed 'clinically suspect arthralgia' (CSA) when a rheumatologist has a high index of suspicion for the development of future clinical joint swelling and subsequently RA) [4], palindromic rheumatism or persistent unclassified arthritis (UA) before eventually developing RA [5]. Whether patients with inflammatory arthritis are categorised as having UA or RA depends in part on which set of RA classification criteria are applied; for example, the 2010 ACR/EULAR criteria tend to classify more patients as having RA than the 1987 ACR criteria [6–8]. Consequently, the symptoms associated with inflammatory arthritis that does not meet the 2010 ACR/EULAR RA (UA 2010) could be subtly different from those associated with inflammatory arthritis that does not meet the 1987 ACR criteria for RA (UA 1987).

Evidence suggests that the earliest clinically apparent stages of RA offer an important therapeutic window, where timely treatment can significantly alter disease progression and outcome [9–11]. Many have extrapolated to propose that treating patients who are symptomatic and at high risk of future RA development may lead to enhanced clinical outcomes. Methotrexate has been shown to delay the onset of 1987 classifiable RA and radiographic progression of disease in 1987 classifiable UA patients [12]. Currently the effects of B [13,14] and T [15] cell-modulating therapy on individuals at risk of RA are being investigated.

Approaches to identify individuals at risk of RA have taken a number of different forms including [1] targeting members of the general population or first-degree relatives of patients with RA and assessing them for RA-related autoantibodies and symptoms and [2] targeting patients who present either to primary or secondary care with musculoskeletal symptoms and quantifying risk on the basis of variables including symptoms and the results of laboratory and imaging tests. Clearly, the pre-test probability of RA development and thus the predictive value of specific risk factors in these scenarios are different. Nevertheless, an understanding of which symptoms are associated with RA development is relevant in all these contexts. As such there is need for more insight into symptoms in those at risk of RA [16–18]. Qualitative approaches provide a valuable opportunity to understand the nature of symptoms in individuals at risk of RA but not without limitations. Reporting of symptoms retrospectively by RA patients are subject to recall bias. Furthermore, contemporaneous symptom reporting can also be problematic as not all individuals will develop RA. Ideally, a longitudinal mixed methods approach would be required to assess differences in symptom complexes between those who eventually develop RA and those who do not. To date, a number of quantitative studies have been undertaken to explore the symptoms in patients at risk of RA and relate these to future RA development. An important limitation of these studies is that the domains across which symptom data are collected are based upon physician's pre-conceptions of what symptoms are likely to be present in at-risk individuals rather than on data from qualitative studies that have captured the symptomatology of at-risk individuals. Such pre-conceptions are largely informed by an understanding of the symptoms associated with established RA, and clinical experience of seeing and following up 'at-risk' individuals, especially those with UA.

The aim of this review is to present literature that has explored symptoms in patients prior to the fulfilment of classification criteria for RA, with a focus on patients with musculoskeletal symptoms prior to the onset of clinically apparent joint swelling.

Data from quantitative research

Quantitative work has been undertaken to explore the symptoms of individuals at risk of RA. Survey questions are largely based on symptoms characteristic of established RA and are therefore assumed to be present in at-risk individuals too [19]. Tables 1 and 2 summarise quantitative work undertaken in patients with musculoskeletal symptoms prior to the onset of clinically apparent joint swelling and patients with UA, respectively.

Common clinical manifestations in symptomatic patients prior to the development of joint swelling include symmetrical pain affecting the upper and lower extremities [20–22], in particular the small joints of the hands [21,22]. A greater proportion of those with early morning stiffness that lasted more than 60 min went on to develop inflammatory arthritis at follow-up [22]. A cross sectional analysis

Table 1
Studies in patients at risk of RA with musculoskeletal symptoms but without clinically apparent joint swelling: quantitative data relating to demographic, clinical and laboratory variables.

	van de Stadt et al. (n = 374) [21]			van Steenbergen et al. (n = 150) [22]			Rakieh et al. (n = 100) [20]	
Inclusion criteria	positive ACPA and/or Immunoglobulin-*M*-RF status and (a history of) arthralgia			Clinically Suspect Arthralgia of the small joints for <1 year that was, according to a rheumatologist, suspected to progress to RA over time			Positive ACPA and new non-specific musculoskeletal symptoms	
Demographical characteristics	Progression to RA (n = 131)	No progression to RA (n = 243)	Hazard Ratio (HR) (95% Confidence Interval [CI])	Progression to inflammatory arthritis (n = 30)	No progression to inflammatory arthritis (n = 119)	HR	Frequency [n/N (%) progressed to Inflammatory arthritis]	HR (95% CI)
Age in years, mean (standard deviation [SD])	47 (11)	49 (12)	0.99 (0.98–1.00)	43.9 (12.7)	43.1 (12.8)	1.004 (0.98–1.03)		
Female, (number [n]) (%)	97 (74)	188 (77)	0.95 (0.64–1.42)	22 (73.3)	87 (73.1)	1.02 (0.45–2.29)		
Family history positive for rheumatoid arthritis (RA), n (%)	38 (29)	48 (20)	1.26 (0.86–1.85)	12 (40)	38 (31.9)	1.37 (0.66–2.85)	11/25 (44)	1.25 (0.64–2.46)
BMI in kg/m^2, mean (SD)				26.7 (6.1)	26.5 (5.0)	1.01 (0.94–1.08)		
Present smoker, n (%)				9 (30)	29 (24.4)	1.28 (0.59–2.79)		
Symptoms characteristics								
Symptom duration in weeks, med (interquartile range [IQR])				17 (8–30)	18 (10–31)	0.99 (0.98–1.01)		
Joint symptoms of recent onset (<1 year)	48 (37)	72 (30)	1.47 (1.02–2.11)				15/31 (48)	1.05 (0.57–1.92)
Gradual symptom onset (>1 week)				22 (73.3)	95 (80.5)	0.68 (0.30–1.53)		
Morning stiffness ≥60 min n (%)	31 (24)	37 (15)	1.94 (1.29–2.91)	15 (50)	38 (33.6)	1.89 (0.92–3.87)	13/22 (59.1)	1.92 (1.02–3.63)
Intermittent symptoms	68 (52)	64 (26)	2.2 (1.56–3.11)				12/20 (60)	1.27 (0.66–2.44)
Visual analogue score (VAS) pain ≥50, n (%)	59 (45)	69 (28)	1.87 (1.32–2.64)				11/25 (44)	1.26 (0.64–2.5)
Small joints n (%)	96 (73)	164 (68)	1.07 (0.72–1.60)	19 (63.3)	107 (90.7)	Not recorded		

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Table 1 (*continued*)

	van de Stadt et al. (n = 374) [21]			van Steenbergen et al. (n = 150) [22]			Rakieh et al. (n = 100) [20]	
Small and large joints n (%)				9 (30)	6 (5.1)	5.28 (2.38–11.73)		
Large joints n (%)				2 (6.7)	5 (4.2)	1.89 (0.44–8.14)		
Upper extremities n (%)				20 (66.7)	88 (73.9)	Nil		
Upper & lower extremities n (%)	80 (60)	109 (45)	1.64 (1.15–2.34)	7 (23.3)	21 (17.6)	1.47 (0.62–3.47)	22/37 (60)	1.38 (0.79–2.41)
Lower extremities n (%)				3 (10)	10 (8.4)	1.36 (0.40–4.58)		
Symmetry n (%)	102 (78)	174 (72)	1.31 (0.87–1.98)	19 (63.3)	91 (77.1)	0.59 (0.28–1.23)		
Laboratory characteristics								
C-Reactive protein (CRP) level in mg/L, med (IQR)				1.5 (0–14.5)	0 (0–4)	1.06 (1.03–1.09)		
hsCRP $\geq$ 2 mg/dL							24/43 (56)	1.27 (0.66–2.42)
CRP level >5 mg/L, n (%)	14 (11)	22 (9)	1.29 (0.73–2.26)	10 (33.3)	21 (17.6)			
Rheumatoid factor (RF)-positive (>3.5 IU/mL), n (%)				18 (60)	15 (12.6)	6.94 (3.34–14.43)	9/15 (60)	1.69 (0.77–3.69)
Anti-citrullinated protein antibodies (ACPA) positive (>7 U/mL), n (%)				16 (53.3)	8 (6.7)	10.07 (4.87–20.82)	50/100 (50)	1.43 (0.64–3.19)
RF and ACPA positive	67 (51)	44 (18)	8.87 (4.79–16.41)					

Table 2
Studies in patients with undifferentiated arthritis: quantitative data relating to demographic, clinical and laboratory variables.

	Duer-Jensen et al. (n = 116) [25]			van der Helm-van Mil et al. (n = 570) [24]		
Inclusion Criteria	>2 tender joints and/or >2 swollen joints among the metacarpophalangeal, proximal interphalangeal, wrist, or metatarsophalangeal (MTP) joints for >6 weeks but <24 months, without a specific rheumatology diagnosis in particular not fulfilling 1987 classification American College of Rheumatology (ACR) criteria for RA.			Newly presenting inflammatory arthritis and not fulfilling 1987 ACR classification criteria for RA or criteria for another classifiable inflammatory arthritis		
Demographical characteristics	RA progression (n = 27)	No RA progression (n = 89)	P-value	RA progression (n = 177)	No RA progression (n = 393)	P-value
Age in years, mean (standard deviation [SD])	50 (21–80)	47 (19–82)	0.74	56.3 (15.3)	48.6 (17.0)	<0.001
Female, number (n) (%)	22 (81.5)	68 (76.4)	0.79	121 (68)	208 (53)	0.001
Family history positive for RA, n (%)				54 (31)	81 (21)	0.01
Present smoker, n (%)				84 (47)	187 (48)	1.0
Symptoms characteristics						
Symptom duration, median (range) months (SD)	4 (2–18)	7 (1.5–24)	0.17			
Symptom duration >6 months				61 (36)	107 (28)	<0.001
Gradual symptom onset (>1 week)				86 (49)	141 (36)	
Morning stiffness ≥60 min, n (%)	14 (51.9)	19 (21.8)	0.01			
Morning stiffness visual analogue score (VAS) (0–100) (SD)				53.3 (30.1)	35.5 (30.0)	<0.001
Rheumatoid nodules, n (%)	0 (0)	0 (0)	1.0			
Pain VAS	49 (12–77)	33.5 (0–98)	0.001			
Small joints, n (%)				95 (54)	171 (44)	
Large joints, n (%)				32 (18)	165 (42)	
Small and large joints, n (%)				50 (28)	57 (15)	<0.001
Upper extremities, n (%)				71 (40)	177 (45)	
Lower extremities, n (%)				22 (12)	139 (35)	
Upper and lower extremities, n (%)				84 (47)	77 (20)	<0.001
Symmetry, n (%)	5 (18.5)	11 (12.4)	0.52	118 (67)	147 (37)	<0.001
Laboratory characteristics						
C-reactive protein (CRP) level in mg/L, med (interquartile range [IQR])				14 (7–13)	8 (3–21)	<0.001
Erythrocyte sedimentation rate, median (IQR) mm/h				32 (19–53)	17 (8–38)	<0.001
Elevated CRP (≥5 mg/L), no. (%)	19 (70.4)	30 (34.1)	<0.01			

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Table 2 (*continued*)

	Duer-Jensen et al. (n = 116) [25]		van der Helm-van Mil et al. (n = 570) [24]
Rheumatoid factor (RF) positive (>3.5 IU/mL), n (%)	16 (59.3)	18 (20.5)	<0.01
ACPA positive (>7 U/mL), n (%)	9 (33.3)	8 (9.0)	<0.01

conducted on a Dutch cohort suggested that increased early morning stiffness correlates with RA development in symptomatic 'at-risk' patients [23].

Similar to patients with musculoskeletal symptoms prior to the onset of clinically apparent joint swelling, patients with UA (not fulfilling 1987 ACR criteria for RA) who eventually develop RA report symmetrical symptoms affecting the upper and lower extremities with prolonged morning stiffness [24,25].

Predictive algorithms including demographic, clinical and laboratory variables have been developed for predicting the development of RA in patients with autoantibody-positive arthralgia [21] and UA (as defined by 1987 ACR criteria for RA) [24,26]. Symptoms are included in the clinical components of each model for respective at risk populations. In patients with seropositive arthralgia, symptoms of recent onset, which were intermittent, affected the upper and lower extremities, and were associated with more than 1 h of early morning stiffness, identified those more likely to progress to RA [21]. Similarly, symmetrical symptoms affecting the upper and lower extremities with severe morning stiffness increased the likelihood of UA patients developing RA [24]. The importance of the location of symptoms has also been highlighted in a prospective cohort study of patients identified in primary care with non-specific musculoskeletal symptoms without clinical synovitis; patients with pain in the wrists, hands, feet and shoulders were more likely to be ACPA positive, although the association between symptoms and progression to RA was not analysed due to limitations in sample size [27].

There is a chance that some critical symptoms (that are either common and or discriminatory) in this early phase were overlooked in these quantitative studies as they were not assessed. Therefore, qualitative studies are important to identify the full range of symptoms associated with musculoskeletal symptoms prior to the onset of clinically apparent joint swelling, which can subsequently be explored in quantitative research to assess relationships with RA development and utility in predictive algorithms.

Data from qualitative research

Qualitative approaches provide an opportunity to explore the full range of symptoms and symptom complexes experienced by individuals during the 'at-risk' stages of RA. Different qualitative methods can be used to capture these data; these could include qualitative interviews and focus groups.

Qualitative data regarding the experience and impact of symptoms have been collected from 15 ACPA-positive patients with arthralgia and from 11 newly diagnosed RA patients [28]. Focus group discussions and semi-structured interviews were guided by an interview schedule developed from a review of the literature and in consultation with patient research partners. An interactive feedback procedure was used between ACPA-positive arthralgia patients and patients newly diagnosed with RA. This process allowed each group of participants to reflect on the experiences of the other group. The patients' symptoms were grouped into six major themes as described below.

Pain in and around the joints was a key symptom. Many symptomatic ACPA-positive patients appeared to experience less intense pain than the early RA patients. Most early RA patients gave an account in which the experience of pain gradually increased in intensity before the diagnosis of RA. Some symptomatic ACPA-positive patients likened the pain to muscle soreness experienced after strenuous exercise. The pain in symptomatic ACPA-positive patients affected sleep and was recurrent in nature, with many patients describing it as 'bothersome' and 'annoying'. Additionally, symptomatic

ACPA-positive patients stated that the onset of pain often followed exertion or some form of mild trauma and was sometimes preceded by tingling sensations around the joints [28].

Joint redness, warmth and swelling represented another important symptom theme. Some symptomatic ACPA-positive patients experienced transient episodes of joint swelling, with burning sensations, warmth and redness of the skin around their joints during episodes of swelling. Patients newly diagnosed with RA also recalled burning sensations around the joints at symptom onset; with the benefits of hindsight, they reported a discrepancy between the pain they experienced and the intensity of their joint swelling at the onset of their symptoms. Some described considerable initial pain in the absence of swelling and that when the swelling eventually developed, at least initially, it was frequently transient and migratory [28].

Joint stiffness was another commonly reported symptom. Some symptomatic ACPA-positive patients described classical morning stiffness, whilst others described stiffness that was worse in the evenings. In some cases, the stiffness was described as 'painful', restricting the range of movement and associated with numbness. Symptomatic ACPA-positive patients noted that stiffness duration increased as their disease progressed [28].

The fourth theme represented **weakness and loss of motor control**. Symptomatic ACPA-positive patients described transient episodes of loss of muscle function that had resulted in falls and objects being dropped; these episodes could occur abruptly and unexpectedly. Other patients described persistent weakness. Some symptomatic ACPA-positive patients reported having to use specialist equipment to aid in activities associated with daily living [28].

Fatigue, sleeping difficulties and depressive symptoms were commonly reported. Extreme fatigue resulting in symptomatic ACPA-positive patients falling asleep or feeling unable to get up from the floor was reported. Patients described pain as an obstacle to sleep, and some patients associated fatigue with the sleeping difficulties they experienced. Some described fluctuations in fatigue with onset heralding the onset of other symptoms [28].

The final theme is related to the **pattern of symptom experience and onset**. Many symptomatic ACPA-positive patients described migratory and palindromic episodes with symptoms lasting for days before dissipating. In contrast, as symptoms progressed towards RA, symptomatic episodes would last longer before eventually persisting without episodes of resolution in between [28].

This qualitative study thus highlighted a constellation of symptoms described by patients, with symptomatic ACPA-positive individuals at risk of RA that have previously not been captured in quantitative work. These included numbness; restricted movements; loss of strength; sudden loss of function (dropping objects); muscle fatigue; muscle cramps; abnormal skin sensations; weight loss; and burning sensation, warmth and redness around the joint.

The symptoms experienced by symptomatic ACPA-positive patients, as outlined above, are burdensome, with considerable physical and psychological impact [29]. Physical impact resulted, in part, from difficulties with hand function and mobility. Tasks such as dressing, washing, eating and household chores were compromised. A common sentiment of apprehension and uncertainty was present as patients did not know if their disease would progress to RA. Such 'at-risk' patients also described low mood and in some cases a considerable psychological impact of their symptoms ('It started in my wrist, moved to my elbow and hands. A terrible pain, you can't hold anything. It lasted for two days. I didn't sleep for nights. I thought if this is my future, then I want to get out' [29]). Patients had specific fears of developing RA and subsequent disease progression leading to life-limiting disability. Patients also experienced, shame, despair and frustration [29]. Interestingly, many of the psychological symptoms experienced were as a result of fear of the unknown as opposed to a consequence of the physical impact of the symptoms experienced at the time. The resulting disability from physical and psychological symptoms of individuals at risk of RA can be profound. A recent study of 255 patients with CSA for less than 1 year showed functional imitations as measured by HAQ comparable to those with early arthritis [30].

A separate focus group conducted with four female CSA patients (three seronegative and one seropositive) explored their perceptions of their condition [31]. Patients described difficulty in performing a range of activities such as putting on shoes, going hiking, shaking hands and avoiding social situations entirely [31]. In addition, patients discussed the effect of CSA on personal control, engaging in health-promoting behaviours such as dietary change and practicing yoga [31]. CSA patients

expressed concern and fear of pain reoccurrence during pain-free periods. There was also fear of disease progression with accompanying symptom amplification [31].

Patients with palindromic rheumatism [32] represent a distinct subset of at-risk individuals, and some data are available regarding the symptoms experienced by patients with this diagnosis. A quantitative study of 39 patients diagnosed with palindromic rheumatism revealed periodic acute onset of joint swelling [32]. Joint swelling typically lasted hours to days (though could last up to two weeks), with asymptomatic periods between episodes [32]. A spectrum of pain was reported, from mild to debilitating. Less common symptoms included fever, which accompanied episodes of arthritis, skin nodules and a change in skin colour over the affected area [32]. A survey conducted on 60 palindromic rheumatism patients revealed similar findings, highlighting that flares tend to be monoarticular [33]. Data from a qualitative study in 17 patients with palindromic rheumatism showed that most patients experienced transient symptoms of progressive intensity [34]. Palindromic flares were characterised by intense pain, followed by swelling of a joint. In addition, patients reported soreness, burning sensations, tenderness, stiffness, warmth and colour change at or around the joint. Less frequently transient nodules, painful skin lesions, fatigue and depression were also described. Symptoms typically evolved over time, increasing in frequency and severity in the majority of patients [34]. The unpredictable nature of the attacks caused psychological and emotional distress. Some patients postulated flares to be triggered by lifestyle factors such sleep deprivation, alcohol, diet and stress [34].

Data from qualitative studies in individuals at risk of RA have been used to inform the development of a questionnaire, which aims to capture the prevalence of these symptoms quantitatively; work on this is currently ongoing [35].

Aetiology of symptoms in patients with clinically suspect arthralgia

Symptoms in individuals at risk of RA are often considerable. Although it is postulated that many of these symptoms can be attributable to synovitis in those with palindromic arthritis or UA, this has not been shown. The explanation for articular and extra-articular symptoms in patients with CSA without clinically identifiable joint swelling is less obvious. One potential explanation is clearly the presence of subclinical synovitis or tenosynovitis, and several studies have investigated this using different imaging modalities.

MRI of the symptomatic joints of the hands and feet in 21 ACPA-positive patients without clinical arthritis revealed evidence of bone marrow oedema and synovitis at symptomatic wrist, MCP, PIP and MTP joints in some but not all patients [36]. Comparable findings have been reported in seronegative CSA patients [37]. A similar study from a different group looking at ACPA-positive arthralgia patients showed that 26 of 28 patients had a RAMRIS synovitis score of at least one in at least one hand or wrist joint, with 10 patients having a synovitis score of at least two in at least one joint [38]. One important consideration in the context of such imaging studies is the frequency of subclinical synovitis in apparently healthy joints. Of the four asymptomatic healthy controls also included in this study, all had an MRI synovitis score of at least one in at least one joint [38]. Whilst subclinical synovitis may be present in many patients with CSA, some patients experienced joint-related symptoms in the absence of such synovitis. Furthermore, such synovitis can be present in healthy individuals without joint symptoms. The relationship between symptoms and subclinical synovitis is thus not straightforward.

A prospective longitudinal study of 150 CSA patients (both seropositive and seronegative) assessed the ability of MRI-detected abnormalities to predict the development of clinically apparent inflammatory arthritis [22]. MRI-detected synovitis, bone marrow oedema and tenosynovitis were all associated with future arthritis development [22]. Importantly, arthritis development was unusual in the absence of subclinical synovitis [22].

Ultrasound has also been used as an imaging modality to assess the presence of synovitis in individuals at risk of RA. Whilst ultrasound evidence of synovitis (both grey-scale and power Doppler) is present in ACPA-positive patients without clinical arthritis [39] and its presence is associated with future arthritis development [39,40], the majority of painful or tender joints in patients with autoantibody positivity and musculoskeletal symptoms did not have ultrasound evidence of synovitis (as judged by the presence of effusion, synovitis or power Doppler) [40].

In addition to ultrasound and MRI, macrophage positron emission tomography has also been used to image ACPA-positive arthralgia patients [41]. Of 29 ACPA-positive arthralgia patients, 4 had a positive PET-CT scan of at least one of the hand or wrist joint. All 4 patients developed RA at follow-up [41].

Thus in a proportion of patients with CSA, including patients with CSA who are known to eventually develop RA, imaging fails to reveal subclinical synovitis. Furthermore, a study of the synovium from autoantibody-positive patients who either had arthralgia or a first-degree relative with RA showed no overt histological synovitis from knee joint synovial biopsies despite the fact that in almost half the patients, the knee joint was symptomatic [42]. Consequently, histological synovitis also does not fully explain the prevalence of joint symptoms in patients with musculoskeletal symptoms and autoantibody positivity at risk of RA. Interestingly, recent data suggests that ACPA itself may play a role in the development of joint-related symptoms in the absence of discernible joint inflammation. Murinised monoclonal ACPA injected into mice gave rise to pain behaviour, with IL-8 pathways implicated, without any visual or histological evidence of joint inflammation [43].

Whilst subclinical synovitis and tenosynovitis may explain some of the joint related symptoms in patients at risk of RA prior to the onset of joint swelling and autoantibodies may play a role in the pain experience in some symptomatic autoantibody positive patients, the explanation for joint related symptoms in all patients with arthralgia who eventually develop RA remains unclear as are the causes of some of the extra-articular symptoms in this patient group.

A EULAR definition of clinically suspect arthralgia

In an attempt to provide clarity and consistency regarding nomenclature, a EULAR-supported initiative has aimed to define CSA with a particular emphasis on symptoms that predict progression to RA [4]. A taskforce of rheumatologists, health professionals, patients and a methodologist approached this using a three-step process. In the first phase, signs and symptoms associated with CSA were agreed upon and weighted according to relevance to distinguish arthralgia that precedes RA from other types of arthralgia. In the second phase, experts reviewed 50 cases of patients previously presenting with arthralgia without clinically detectable arthritis. Of these, 26 patients had been classified by the treating rheumatologist as having CSA. The experts were blinded to this classification and were presented with clinical data relating to the parameters selected in phase one. The experts were then asked to classify the patient as CSA or non-CSA and to provide a level of confidence in their classification using a numerical rating scale. In phase three, data were collected from new patients with and without CSA (according to the managing rheumatologist) to validate the parameters selected from phase two, resulting in characteristics, including symptoms (see Box 1), which describe CSA at risk of RA development [4].

Box 1
EULAR symptoms describing CSA at risk of RA development.

History taking:

Joint symptoms of recent onset (duration <1 year)
Symptoms located in MCP joints
Duration of morning stiffness ≥60 min
Most severe symptoms present in the early morning
First-degree relative with RA

Physical Examination:

Difficulty making a fist
Positive squeeze test of MCP joints

Summary

This review has highlighted a wide range of symptoms experienced by individuals at risk of RA. These include not only the articular symptoms widely recognised to be associated with established RA (e.g. pain, swelling, stiffness) but other symptoms including joint redness, weakness and loss of motor control, sleeping difficulties, fatigue and depressive symptoms. These symptoms are not only important for clinicians in the context of prognostication but have far reaching physical and psychological consequences for the patient, which should be addressed during their clinical management.

A better understanding of symptoms in individuals at risk of RA will help inform public health campaigns, highlighting relevant symptoms that should prompt presentation to primary care givers. The need for this is illustrated by studies such as that by Van Nies et al., which found that a significant proportion of individuals at risk of RA with subacute disease courses postponed seeking medical help as they thought their disease would be self-limiting [44–46]. Public health messaging to address this, recognising the frequently subacute nature of the onset of RA, may promote rapid help seeking. Furthermore, the optimisation of the selection of symptoms to include in algorithms to predict the development of RA in patients with CSA, palindromic rheumatism and UA should improve the performance of such algorithms and consequently the management of these patients.

Research agenda

1) Further quantitative work should be undertaken in both primary and secondary care, building on published qualitative data, to identify those symptoms that differentiate patients with musculoskeletal symptoms who will eventually develop RA from those who will not.

Practice points

1) Many patients who eventually develop RA present with musculoskeletal symptoms in the absence of joint swelling.
2) Relevant symptoms include those typically associated with established RA such as joint pain and stiffness. Other symptoms include colour changes to the skin around the joints and transient nodules.
3) Many of these symptoms have been incorporated into algorithms that predict the development of RA in patients with RA-related autoantibodies, clinically suspect arthralgia and undifferentiated arthritis.

Conflict of interest

No conflict of interest declared.
Submission declaration – this work has not been submitted/published elsewhere.

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