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Symptom Complexes at the Earliest Phases of Rheumatoid Arthritis: A Synthesis of the Qualitative Literature

REBECCA J. STACK,¹ MELANIE SAHNI,² CHRISTIAN D. MALLEN,³ AND KARIM RAZA¹

Objective. Understanding the features and patterns of symptoms that characterize the earliest stages of rheumatoid arthritis (RA) is of considerable importance if patients are to be identified and started on treatment early. However, little is known about the characteristics of symptoms at the onset of a disease that eventually progresses to RA.

Methods. A systematic review of qualitative peer-reviewed publications was conducted to identify the earliest symptoms associated with the onset of RA. A total of 1,736 abstracts were searched to identify relevant publications. Twenty-six publications were identified, assessed for quality, and subjected to analysis informed by thematic and grounded theory frameworks.

Results. Several interacting themes describing the early symptoms of RA were identified, including swelling, pain and tenderness, stiffness, fatigue and weakness, and the emotional impact of symptoms. For each symptom, different and evolving intensities were described; in some cases, patterns of symptom onset and symptom complexes at the onset of RA were highlighted. Importantly, this review has emphasized major deficiencies in the literature. None of the studies reviewed originally aimed to explore symptoms at RA onset (often discussions about symptom onset were secondary to the study's primary aim). Also, many of the articles identified sampled people diagnosed with RA many years previously, making their recollection of symptoms at onset less reliable.

Conclusion. In order for clinicians to fully understand the earliest phases of disease, the nature of symptoms at onset needs to be understood. The current work represents a useful starting point, but this area needs further qualitative investigation, followed by quantitative explorations of symptom clusters and their associated features.

INTRODUCTION

The rapid identification of patients with rheumatoid arthritis (RA) is vital. Irreversible joint damage can occur during the early stages of disease, and the first 3 months following symptom onset represent a critical therapeutic window during which time drug treatment is particularly effective at controlling synovitis and limiting long-term

joint damage (1–4). Recognizing this, algorithms have been developed and validated to predict the development of RA in patients with newly presenting unclassified arthritis (5,6). In addition, the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA have been developed to facilitate the early identification of patients with inflammatory arthritis requiring disease-modifying

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Significance & Innovations

- This systematic review of the qualitative literature identified what is currently known about the symptoms, and patterns of symptoms, that characterize the earliest phases of rheumatoid arthritis (RA), in particular swelling, pain and tenderness, stiffness, fatigue and weakness, and the emotional impact of symptoms.
- Importantly, this review also highlighted the major deficiencies in the current literature and that additional qualitative research focused on exploring the nature of symptoms in the earliest phases of RA is needed.

therapy (7). Typical features of established RA, including joint pain and swelling (with a characteristic joint distribution) and morning stiffness, are key features of these predictive algorithms and classification criteria.

Since attention has focused on progressively earlier phases of RA, it has become increasingly clear that for many patients there is a prodromal phase associated with joint pain, and sometimes the presence of autoantibodies, before the development of clinically overt synovitis (8). The nature of symptoms during the earliest phase of disease can influence how quickly patients present to professionals and are started on disease-modifying treatment (9). However, the full range of symptoms that characterize this phase, and the phase of early unclassified arthritis, has not been well studied. Cohort studies addressing these phases typically capture and report data on a limited number of symptoms known to be associated with established RA (e.g., joint pain, joint swelling, and morning stiffness). In doing this, it is possible that key symptoms and symptom complexes, specific to these early phases and therefore potentially relevant to the prediction of RA development, and treatment responses are overlooked. The fact that the synovium is histologically normal in patients with joint pain and anti-citrullinated protein antibody positivity (10) suggests that pathologic processes operating during this phase may be different from those operating in established RA; the symptoms associated with these phases may also be different.

The importance of understanding the initial symptoms and symptom complexes in patients with a new onset of a disease that will evolve into RA has been highlighted in several recent reports, including from the EULAR Study Group on Risk Factors for RA (8,11). To address the symptoms of the earliest phases of RA in a systematic way, the full range of symptoms experienced by patients with RA at

the onset of their disease needs to be explored in a qualitative manner. Qualitative data then can be used to inform the development of questionnaire items for use in quantitative studies. The recent emergence of “fatigue” as a key disease outcome measure in established RA is a testament to the importance of exploring the patient’s perspective in the context of the range of symptoms of RA, and to the fact that relying on expert health professional opinion in the absence of patient opinion can lead to important symptoms being overlooked (12).

We have systematically reviewed published qualitative research exploring patients’ experiences of the symptoms of RA at the onset of their disease. Our synthesis of these data highlights what is already known about this area and importantly identifies the deficiencies in the current literature, emphasizing where further research is needed.

MATERIALS AND METHODS

Inclusion criteria. Qualitative studies using an interpretative paradigm to understand the descriptions of symptoms experienced by adults (ages >18 years) at RA onset were included. The definition of symptoms used in this search was physical or psychological signals that indicated a change from normal functioning or health or indicated the presence of illness. The search was restricted to peer-reviewed publications in English.

Search strategy. The search was restricted to published peer-reviewed articles. Abstracts were excluded, since quality indicators were frequently not included in abstracts and primary data (i.e., quotations from participants) were presented in only a very limited way, if at all. The following databases were searched to identify relevant articles: Ovid MEDLINE (PubMed; 1950 to June 2012), CINAHL (1937 to June 2012), and PsycINFO (1806 to June 2012). The search terms shown in Table 1 were used. When multiple publications of the same data reporting similar findings were identified, one exemplary publication was selected.

Analysis. Selected publications were critically assessed for methodologic quality using established criteria (13,14). As with other published syntheses, we chose an inclusive strategy, evaluating all studies that contributed relevant data (15,16). Detailed information about the aims, samples, methodologies, and quality indicators of the included studies is shown in Table 2. Each article was initially independently coded by 2 authors (MS and RJS). Initial coding was applied to first-order constructs, where the

Table 1. Search terms used for systematic synthesis

Symptom(s) OR Onset OR Early OR Fatigue OR Pain OR Stiffness OR Swelling	AND	Arthrit* OR Rheumat* OR Synovitis	AND	Qualitative
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Table 2. Summary of articles identified through the systematic search that met the criteria for the systematic synthesis and from which data were extracted*

Author, year (ref.)	Country	Aim	Sample characteristics: 1) no., 2) sex, 3) disease duration, 4) definition and diagnosis of RA	Qualitative method and analysis used	Quality check
Backman et al, 2007 (35)	Canada	To explore the impact of chronic inflammatory arthritis on parenting and to develop a conceptual framework for subsequent study of mothering	<ol style="list-style-type: none"> 6 participants with RA (6 participants with other inflammatory arthropathies were also sampled) 6 women Not specified for the 6 patients with RA (overall range for the 12 patients was 3–40 years) Rheumatologist's diagnosis (use of classification criteria NR) 	In-depth semistructured interviews, analyzed using grounded theory	Transcripts were independently reviewed by 2 researchers Member checking was undertaken with 1 participant checking results
Bernatsky et al, 2010 (40)	Canada	To identify barriers to optimal care for individuals with RA	<ol style="list-style-type: none"> 18 participants with RA (54 health care professionals also sampled) 13 women NR Rheumatologist's diagnosis (use of classification criteria NR) 	Structured focus groups analyzed using content analysis (analysis reported also to draw on grounded theory principals)	Transcripts were independently coded Results were viewed by stakeholders to confirm validity
Brown and Williams, 1995 (31)	UK	To explore women's experiences of RA	<ol style="list-style-type: none"> 7 participants 7 women NR Sample consisted of inpatients admitted due to symptoms of RA (use of classification criteria NR) 	Conversational interviews guided by an interview schedule; data were interpreted using narrative analysis	NR
Bury, 1982 (23) and Bury, 1988 (28)	UK	To explore the problems of recognition and challenges in life situations and relationships occasioned by the development of RA	<ol style="list-style-type: none"> 30 participants 25 women Participants were new referrals to secondary care (exact disease duration NR) A "definite diagnosis [of RA] was . . . confirmed" in 29 patients (use of classification criteria NR) 	Semistructured interviews with followup interviews; analysis informed by narrative approaches	Themes uncovered were validated against theoretical models
Dildy, 1996 (36)	US	To explore the nature of suffering in people with RA	<ol style="list-style-type: none"> 14 participants 9 women Range 6 months to 35 years from time of diagnosis Physician's diagnosis (use of classification criteria NR) 	Interview process was described as an "intense interview strategy" with followup interviews; analysis informed by grounded theory	2 researchers examined data to establish reliability and consistency in coding Findings were validated and confirmed with the informants through the second telephone interview (continued)

Table 2. (Cont'd)

Author, year (ref.)	Country	Aim	Sample characteristics: 1) no., 2) sex, 3) disease duration, 4) definition and diagnosis of RA	Qualitative method and analysis used	Quality check
Fair, 2003 (42)	US	To investigate explanations of RA from women's perceptions of the illness experience and providers' understanding of disease	<ol style="list-style-type: none"> 17 participants 17 women NR Physician's diagnosis (use of classification criteria NR) 	Semistructured interviews supported by field notes; thematic analysis and framework approaches drawn upon	Member checking: participants were sent copies of the explanations of RA. Dependability or reliability of the study maintained by audit trail reviewed by 4 independent researchers NR
Griffith and Carr, 2001 (19)	UK	To explore the experiences of coping with RA	<ol style="list-style-type: none"> NR NR NR NR 	In-depth interviews; method of analysis NR	NR
Hewlett et al, 2005 (41)	UK	To explore the concept of fatigue as experienced by RA patients	<ol style="list-style-type: none"> 15 participants 12 women Range 1.5–30 years (mean 12.6 years) from time of diagnosis 1987 ACR classification criteria for RA fulfilled 	Face-to-face semistructured interviews, analyzed to establish themes grounded in data	Interviews were transcribed individually by 2 researchers independently 5 random transcripts were analyzed independently by 2 external researchers Codes were also reviewed by a steering committee
Hwang et al, 2004 (38)	South Korea	To explore and describe the illness experience of women with RA	<ol style="list-style-type: none"> 5 participants 5 women Range 4–12 years (mean 7 years) Participants were diagnosed with RA in secondary care (use of classification criteria NR) 	Informal unstructured interviews were undertaken; phenomenological analysis of data	Member checking: participants checked the transcripts to ensure that an accurate representation of their experience was gathered
Kumar et al, 2010 (21)	UK	To assess the reasons underlying delay in consultation in RA patients from a South Asian background	<ol style="list-style-type: none"> 10 participants 9 women Participants were newly presenting to secondary care with RA 1987 ACR classification criteria for RA fulfilled 	Face-to-face in-depth semistructured interviews, analyzed using grounded theory analysis	Member checking: by providing participants with a verbal summary of the areas covered and themes identified in the interview
Lempp et al, 2006 (20)	UK	To explore direct personal experiences of living with RA and the impact of the illness upon patients' lives	<ol style="list-style-type: none"> 26 patients 22 women Range 1–29 years (mean 10 years) Participants were secondary care patients with RA (use of classification criteria NR) 	Face-to-face in-depth semistructured interviews, analyzed using content analysis	Plausibility of accounts judged by authors, cross-referencing of themes with an independent researcher

(continued)

Table 2. (Cont'd)

Author, year (ref.)	Country	Aim	Sample characteristics: 1) no., 2) sex, 3) disease duration, 4) definition and diagnosis of RA	Qualitative method and analysis used	Quality check
Neill, 2002 (24)	Australia	To explore patterns in the life stories of women living with RA	<ol style="list-style-type: none"> 3 participants 3 women Range 19–38 years (symptom duration) NR 	4 face-to-face unstructured interviews with each participant, supported by photos, field notes, and telephone calls; analysis drew on pattern and theoretical analysis techniques	Repeated interviewing to explore concepts in depth and validate initial interpretations
Nyman and Lützen, 1999 (30)	Sweden	To identify the caring needs of women with RA undergoing acupuncture treatment	<ol style="list-style-type: none"> 6 participants 6 women Range 4–26 years (median 11 years) from time of diagnosis Rheumatologist diagnosis (use of classification criteria NR) 	20 semistructured interviews over a period of 11 weeks, conducted during acupuncture sessions; data analyzed using content analysis	Authors suggested that data were validated, but the method of validation was not explained
Oliver et al, 2008 (22)	UK	To explore the experiences of those with RA in order to understand the impact on the individual and on health care resources	<ol style="list-style-type: none"> 22 participants 16 women ≤3 years from time of diagnosis Participants were asked to confirm with a health care professional that they had seropositive RA (use of classification criteria NR) 	Telephone semistructured interviews, analyzed using thematic analysis	Process maps were transcribed into individual participant maps and returned to the participant for verification and alteration Themes reviewed by research team
Sakalys, 1997 (29)	US	To explore prediagnostic illness behavior in RA	<ol style="list-style-type: none"> 50 participants 20 women ≤2 years from time of diagnosis 1987 ACR classification criteria for RA fulfilled 	Structured interviews; data were analyzed using content analysis	Intercoder agreement was checked periodically
Sheppard et al, 2008 (25)	UK	To explore people's beliefs, feelings, and actions at the onset of RA to gain insights into the factors that influenced their decision to consult	<ol style="list-style-type: none"> 24 participants 10 women ≤14 months from time of diagnosis 1987 ACR classification criteria for RA fulfilled 	In-depth semistructured interviews; analysis followed a grounded theory approach	Blind and independent coding Self-selecting participants were sent a summary of the interview
Schneider et al, 2008 (27)	South Africa	To explore a range of experiences, including onset of disease, treatment, environmental barriers and facilitators, employment, and social inclusion	<ol style="list-style-type: none"> 60 participants 60 women Range 1–26 years (or more) since time of diagnosis 1987 ACR classification criteria for RA fulfilled 	Semistructured in-depth interviews, analyzed using a thematic analysis approach	NR

(continued)

Table 2. (Cont'd)

Author, year (ref.)	Country	Aim	Sample characteristics: 1) no., 2) sex, 3) disease duration, 4) definition and diagnosis of RA	Qualitative method and analysis used	Quality check
Shaul, 1995 (17)	US	To explore how women manage RA and the demands of their everyday lives	<ol style="list-style-type: none"> 30 participants 30 women ≤18 years from time of diagnosis "Definite, classical or probable RA" as assessed by a rheumatologist 	Semistructured interviews, analyzed using constant comparative methods	Interview guide assessed for face validity by 2 women with RA Independent coding of a sample of transcripts
Shaul, 1997 (33)	US	To explore the transition of women experiencing RA	<ol style="list-style-type: none"> 30 participants 30 women ≤18 years from time of diagnosis "Definite, classical or probable RA" as assessed by a rheumatologist 	Semistructured interviews, analyzed using constant comparative methods	Interview guide assessing for face validity by 2 women with RA Independent coding of a sample of transcripts
Stamm et al. 2008 (39)	Austria	To explore the life story of people diagnosed with RA	<ol style="list-style-type: none"> 10 participants 8 women NR Attendees at a rheumatology outpatient clinic (use of classification criteria NR) 	Repeated narrative interviews were analyzed using a narrative biographical method	Self-reflection and debriefing were undertaken and findings were discussed with coauthors
Townsend et al, 2010 (26)	Canada	To identify ethical challenges in the early RA experience	<ol style="list-style-type: none"> 8 participants NR ≤12 months from time of diagnosis Physician's diagnosis (use of classification criteria NR) 	In-depth interviews, including followup interviews; constant comparisons and thematic analysis	Blind and independent coding of transcripts
Wiener, 1975 (34)	US	To explore the management of pain in RA	<ol style="list-style-type: none"> 21 participants NR NR NR 	Interviews and observational data were collected; analysis informed by grounded theory	NR
Williams, 1984 (18)	UK	To explore the way in which beliefs about the etiology of arthritis can be understood in terms of narrative reconstruction	<ol style="list-style-type: none"> 30 participants 19 women ≥5 years NR 	In-depth semistructured interviews; analysis informed by narrative approaches	Themes uncovered were validated against theoretical models
Williams and Graham, 2012 (37)	UK	To explore patients' experiences of foot problems associated with RA	<ol style="list-style-type: none"> 22 participants 16 women Mean 15 years for women and 13 years for men RA according to 1987 ACR classification criteria 	Focus groups facilitated by a researcher; analysis of data informed by thematic analysis	Transcripts were read and verified by 1 participant from each focus group
Yoshida, 1996 (32)	Canada	To explore various forms of uncertainty among people with RA	<ol style="list-style-type: none"> 46 participants 32 women Range 18 months to 53 years (mean 13.5 years) Participants were members of the consultation and therapy service of the arthritis society (use of classification criteria NR) 	In-depth semistructured interviews; data were analyzed using a constant comparative approach and grounded theory methods	Coding scheme was developed and refined by 2 researchers

* RA = rheumatoid arthritis; NR = not reported; ACR = American College of Rheumatology.

initial coding of participants' quotations was undertaken, and to second-order constructs, where the key findings and interpretations of the articles' authors were coded. Coding of first- and second-order constructs was extracted and used to describe the relevant themes in each article. All initial codes were categorized and labeled under broad headings. To develop reliable and broader themes, the initial independently derived codes were triangulated between researchers (RJS, MS, and KR). Coding categories that lacked concordance were discussed and finally absorbed into the overall coding framework. Concepts that were common across studies were identified and summarized, and subsequently grouped according to overarching themes. These were rechecked by 2 authors (MS and RJS), who re-read all relevant articles, adjusted themes, and also incorporated illustrative quotations.

RESULTS

The search strategy identified 1,736 peer-reviewed publications (excluding duplicates). The abstracts of all articles were read to identify studies potentially meeting the inclusion criteria. Subsequently, 91 abstracts were identified as potentially relevant, and each article was read in full by 2 authors (MS and RJS). Twenty-six publications were included in the final analysis (Table 2). Most studies were from either Europe or North America. The majority of participants sampled across individual studies were women, with some studies exclusively focusing on the perspectives of women with RA. Importantly, no studies had, as their primary aim, the exploration of symptoms at the onset of RA. In addition, most studies explored issues surrounding the onset of symptoms many years after participants had been diagnosed with RA. The methodologic quality of the majority of articles reviewed was high. Methods included in-depth methods and validity checks, including blind coding and respondent validation. Only 4 studies reported no checks on the validity of the data collected (Table 2).

Themes. Five major themes were developed describing the physical and, to a lesser extent, the psychological symptoms experienced at the onset of RA: swelling, pain and tenderness, stiffness, fatigue and weakness, and the emotional impact of symptoms.

Concepts that cut across all of these "symptom" themes were descriptors of the intensity of each of these symptoms and their speed and pattern of onset as well as complexes of symptoms, either occurring together from onset or gradually accumulating over time. In addition, there were frequent descriptions of the development of symptoms following pregnancy, functional impairment associated with early symptoms, and the impact of early symptoms on social relationships and work. These are not systematically reported here because we regarded them as reflecting the causes and consequences of symptoms rather than being symptoms themselves.

Theme 1: swelling. Swelling was described as the joint becoming "puffed out" (17,18). The feet and hands were

most often affected (18,19). Swelling was often described as severe; one woman found the swelling in her feet was so bad at the onset of RA that she had begun to wear her husband's slippers (20). The impact of swelling in the small joints was often described in the context of its effect on day-to-day activities such as walking, gripping, writing, and cooking (18).

"I couldn't even make the chapatti. The swelling had gone really worse and I thought I have to go to the GP [general practitioner]" (21).

"My feet began to swell and my hands began to swell. I couldn't hold a pen, I had difficulty getting between machines and difficulty getting hold of small things" (18).

"Aware of swelling to fingers of the right hand . . . waited two weeks to see if condition improved" (22).

"I noticed that my feet and ankles started to swell and I thought, I am doing too much walking" (21).

"Then one day, all of a sudden my joints all swelled up. All over. And they were so tender and horrible. My legs swelled up and my hands were so sore I couldn't touch anything. When my feet swelled up, I finally went to the doctor" (17).

Bury highlighted that symptoms (such as swelling and pain) often "creep up," with a transition from trivial symptoms to severe symptoms associated with significant functional impairment (17,23,24).

"To begin with I thought I had sprained my wrist, 'cos my wrist went as you normally do if you sprain it, it hurt and it became swollen a little bit, so I stuck a wrist strap on it and carried on. It did not get any better for a week and a half, but then the swelling started from the wrist into the back of the hand . . . and that all swollen up until it got quite large. Now, at that stage, I thought well I had better go up and see the doctor" (25).

In some cases, it was reported that other symptoms (such as pain) were present before swelling occurred (25–28). For example, the quotation below suggests that the individual was experiencing problems before their swelling appeared.

"I think I probably would have tolerated it for a while . . . I was trying to figure out what was going on because I had been seeing my physiotherapist on a regular basis and, I finally noticed myself one night that my legs seemed swollen, which kind of said to me, you know: 'Is there a blood pressure thing going on here, or what's going on here?'" (26).

However, this was not always the case. In some instances, it was suggested that swelling occurred first and that joint pain occurred later (19,21).

"My fingers all of a sudden started to swell. Then gradually these became very painful. I thought it was because of the heat. It was summer time, and you know how your feet swell sometimes and that was my thought" (21).

Theme 2: pain and tenderness. Where the onset of RA symptoms was slow, descriptors such as “diffuse,” “gradual,” or “episodic” were used to describe symptoms (24,29). In these circumstances, pain was often described as “mild,” “vague,” and “non-disabling,” making it very difficult for people to understand its cause (with some attributing their symptoms to exertion or minor trauma) (30,31). The vagueness of symptoms was emphasized, with symptoms being described as “everyday aches and pains” (25,30,32) or “twinges” (17,33). These early symptoms were described as a nuisance (23), but usually became more severe and were then associated with functional impairment (17,21,23,27,33).

“It was harrowing. When I got up in the morning my feet were so painful I couldn’t stand on them. I would slide out of bed and with my elbow and rump get into the bathroom. I learned to turn the faucets with my elbows” (34).

Although pain sometimes came on insidiously, a rapid onset was also often reported (17,18,25–27,33). Rapid-onset symptoms were described as “new resistant,” “severe,” “abnormal,” and “debilitating” (26,35). A rapid onset of pain was often associated with the onset of additional symptoms and led to rapid help seeking (29). The suddenness and extreme nature of RA onset in some patients was described as a “light switch” or being “cut off” (36).

“My illness started like someone turned a light switch on one day. All I can remember, it was like a light switch went off” (36).

“In my case, I guess if it was a real gradual thing it wouldn’t be so bad, but like it was it was pretty hard to take just to be cut off all at once like I was. The last day that I worked out there I never felt better in my life. And the next day I never felt worse in my life. . . . It just, it was pretty hard to take” (36).

In such situations, severe pain was defined with descriptors such as “unbearable” or “overpowering” (21,36). One person likened the pain to “bone cancer” (25), and another believed the origin of the pain was a broken or chipped bone (23).

“Well at first I thought I’d broken, chipped the bone in the finger, with it being a knuckle. I thought, I bet I’ve banged it, really, because I do bang my hands a lot sometimes and I thought I’d chipped it and I thought, ‘oh it’ll go off’” (23).

“It was crazy, I used to cry with the pain that’s how bad it was” (21).

“I just found that I was in the most intense pain I’ve ever been in” (19).

In some cases, symptoms were transient (palindromic) in nature (18,33), with some patients describing intermittent episodes of intense pain (31). Migratory pain was also described (19).

“The next morning I had an awful pain in my shoulder. However, eventually it went away and during the next twelve months I had a traveling rheumatism, all round the joints” (19).

Pain was described in a number of locations, most frequently in the feet (including the balls of the feet and toes) (22,28,34,35,37) and hands (22,34,35). Symptoms in the large joints (shoulder, knee, elbow, and hip pain) were described less frequently (22,28).

It was noted that 8 studies described the onset of RA symptoms or severe aggravation of early RA in the postnatal period (17,21,22,28,30,33,35,38).

Theme 3: joint stiffness. General stiffness was less commonly described across the literature, and where it was described, descriptions were brief (24). Also, there were no descriptions of the meaning of stiffness, nor were attempts found to deconstruct the concept of stiffness at RA onset. On occasion, stiffness was briefly mentioned in combination with other symptoms such as “fatigue, morning stiffness and swollen knee” (33). At onset, stiffness was a symptom that could be bothersome at night because it prevented sleep (21).

“I stayed with a family, and in London they did so many things with us. But I noticed only afterwards how much stiffness and rigidity there was” (39).

Aches and pains in the morning were described by a participant in the study by Griffiths and Carr; however, the word “stiffness” was not specifically used (19).

“In my own mind I knew I had something like that, because my joints were aching and creaking, and I was full of aches and pains in the morning when I got up” (19).

However, in 3 studies, stiffness was a specific problem for patients (20,26). In these cases, stiffness was notable because it was localized to a specific area of the body, e.g., the shoulder or neck (20,31). In another instance, palindromic episodes of stiffness and swelling were described (28).

“I didn’t really notice that I had symptoms. I had a stiff shoulder . . . I had a heavy coat . . . I had trouble getting it on and off . . . my daughter had helped me taking it off already but I needed to get it back on” (26).

“I went to the doctor because I had a stiff neck, and she said: ‘Oh I think it’s to do with your neck,’ so she gave me pain killers. And six weeks later I went back again no difference, still in terrible, terrible pain” (20).

Theme 4: fatigue and weakness. A general sense of weakness was described by some people at the onset of RA (28). Some described generalized “flu-like” symptoms, but were not explicit about the specific symptoms that comprised this experience (40).

In addition, descriptions of weakness in the affected extremity and fatigue were identified (17,19,21,33,39,41). Stamm et al described the experience of a person who was suddenly unable to lift his tray in the canteen, and he was unable to drive home that day (39). Others described only noticing the increasing weakness after being unable to undertake routine daily activities, with one person drop-

ping a number of bowls while preparing dinner, and another described being unable to lift a baby (21). In other instances when weakness was mentioned, it was suggested to be a mild problem (25).

“As months went by I noticed that I couldn’t lift my baby very well. It was difficult to dress and feed her” (21).

“First noticed there was a problem, there was a weakness in the hands. Just slight weakness” (25).

Hewlett et al described fatigue as a very important symptom at the onset of RA (41). For one person, weariness was one of the most significant problems faced at the onset of symptoms.

“But what I do remember about the beginning of the rheumatoid arthritis was the massive weariness being almost, almost the biggest symptom” (41).

In addition, sleep disturbance was a common feature and may have aggravated the symptoms of fatigue. People described symptoms interfering with and preventing sleep (19,21).

“When I noticed it was preventing me doing things and it interfered in my sleep, it woke me during the night, then I thought, gosh, this is not right, something needs to be done about this” (21).

“I must have woken in the middle of the night with a vicious pain in my right elbow, which travelled down my fingertips and I just couldn’t sleep; I just walked the floor” (19).

“It used to take me a good couple of hours before I could do anything really. It was keeping me awake at night” (21).

Theme 5: emotional impact. The emotional impact of symptoms at the onset of RA was noted in several studies (19,29,32,33,42). For some, the symptoms were associated with feelings of depression and suicidal thoughts, while others described anger or feelings of fearfulness.

“I used to get real, real depressed. Very depressed. And there were times I would just lay in bed you know thinking, you know, well what is wrong with me” (29).

“I felt suicidal before I came in here; I didn’t know what to do with it. I think it was more I didn’t know what it was” (19).

Yoshida suggested that when the onset of symptoms was rapid, feelings of fear were greater (32). In the early stages of RA where the onset of symptoms was slow, uncertainty about the significance of symptoms was described. Bury described how an insidious onset and fluctuating symptoms created ambivalence and indecision (28). Others suggested that the ambiguity and vagueness of symptoms were related to uncertainty and in some cases, emotional upset (31,32).

“I went through the whole summer not well, sick and I’d keep going back to the doctor and she couldn’t figure out what was wrong with me and I was getting upset with it” (32).

For those experiencing high levels of uncertainty or uncertainty over a long period of time, the eventual diagnosis of RA provided some relief (32), validating the symptoms experienced and confirming that they had physical origins.

“I was relieved to know that it was not in my mind [laugh], that I was not going crazy” (32).

DISCUSSION

Understanding the features and patterns of symptoms that characterize the earliest stages of RA is of considerable importance. Primary care physicians, for whom patients with articular/periarticular pain make up a considerable proportion of their workload, need to be able to identify symptoms and patterns of symptoms that most accurately predict the development of RA and that should guide decisions about further investigation and referral to rheumatologists. Even within secondary care, the ability to predict the development of RA in patients at risk is an important aim, and an understanding of the role of patients’ symptoms in this process needs detailed consideration.

In this review, we have identified 5 major symptoms describing patients’ experiences at the onset of their RA. For each of these symptoms, different and frequently evolving intensities were described, different patterns of symptoms were described (rapid onset and gradual onset, gradually progressive and palindromic), and different complexes of symptoms, at onset and during evolution, were noted. However, perhaps most importantly, this review has highlighted major deficiencies in the current literature in relation to this area. We were able to identify only a small number of relevant qualitative articles. Importantly, none of the studies set out specifically to examine the full depth and breadth of initial symptoms, their nature, and their evolution over time, and the coexistence of symptoms in symptom complexes. Furthermore, characteristics of patients included in the studies were often poorly described, men were significantly underrepresented, and few participants were from nonwhite populations. These issues are important, since sociodemographic differences in the experience of illness have been reported, e.g., people from different ethnic backgrounds have been shown to experience illness in different ways (43). Interestingly, people with RA from a South Asian background delay in seeking help for a longer period of time than white British patients (21). Whether this is because of a different initial symptom experience or because their response to those symptoms differs has not been fully elucidated. One of the most important deficiencies in the current literature is that patients were frequently interviewed many years after the onset of their RA, when their recollections of initial symptoms may have been poor or colored by more recent symptom experiences. Ideally, explorations of early RA symptoms should be carried out in patients shortly after a diagnosis of RA. In addition, exploring symptom experience in symptomatic individuals at risk of RA may help to avoid the drawbacks of retrospective data and help to fully characterize the range of initial symptoms at different phases of disease.

We note that symptoms occasionally reported by patients with established RA (e.g., numbness [44], tingling [45], jaw pain [46], and symptoms of restless legs and leg cramps [47,48]) were not found in the literature included in this review, which focused on disease onset, and the presence of these should be explored in further qualitative work. A systematic review of the symptoms of established RA has yet to be undertaken; however, it is important to consider the symptoms identified in the present review in relation to the symptoms that are recognized to be associated with established RA. Particular symptoms of established RA have been identified as being indicators of disease activity and for distinguishing RA from other inflammatory arthritides. Therefore, joint swelling, tenderness, and pain are key features of disease activity measures and of measures to assess change in disease activity (49–51). Furthermore, the patient perspective has highlighted fatigue as an important disease activity indicator (41,52). However, although disease activity measures capture information on clinically important symptoms, they do not, and are not intended to, capture the breadth of symptoms that an individual with established RA may experience. Work to define a flare of established RA has identified a broader range of symptoms that characterize periods of worsening disease activity, including sleep disturbance, systemic disturbance, stiffness, emotional distress, and reduction in function and participation (53–55). Furthermore, classification criteria for RA have incorporated a range of symptom-related characteristics, including morning stiffness and joint swelling (1987 ACR criteria) as well as joint tenderness (2010 ACR/EULAR criteria) (7,56). Classification criteria aim to distinguish patients with one condition from those with another, and therefore will include only the most discriminatory symptom variables rather than the totality. However, these comparisons demonstrate that many of the symptoms identified in early disease are also key features of established RA.

Once results are available from formal qualitative studies of the emergence of symptoms in people at risk of RA and in those with a new onset of disease, these results can be used to inform the development of a “symptom questionnaire” to assess the frequency of symptoms and their evolution in individuals at risk of RA. Through this approach, refinement of algorithms for use in secondary care to predict RA development in patients with unclassified arthritis (6) and patients with inflammatory joint symptoms and RA-related autoantibodies (57) may be achieved. Importantly, tools also need to be developed for use in primary care to direct management pathways, including determining which patients with joint-related symptoms should be investigated (e.g., with autoantibody testing or imaging) and who should be referred to a rheumatologist (58). The patient’s history is readily available and inexpensive. Maximizing value from this history and assessing the predictive utility of its components in the earliest phases of RA can only be achieved once these components are fully understood.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors ap-

proved the final version to be published. Dr. Stack had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Stack, Sahni, Mallen, Raza.

Acquisition of data. Stack, Sahni.

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