Symptom complexes in patients with seropositive arthralgia and in patients newly diagnosed with rheumatoid arthritis: A qualitative exploration of symptom development

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Running title: Symptom complexes at the onset of RA

ABSTRACT

Objective: The aim of this study was to explore symptoms and symptom development during the earliest phases of rheumatoid arthritis (RA) in patients with seropositive arthralgia and patients newly diagnosed with RA.

Methods: Interviews were conducted with fifteen seropositive patients (anti-CCP positive, and often with arthralgia) and eleven newly presenting RA patients (classified according to 2010 ACR/ EULAR criteria). Feedback procedures shared the experiences of seropositive arthralgia patients with early RA patients and vice versa. Data were analysed using thematic analysis.

Results: Symptoms common to both groups included joint pain, psychological distress, muscle cramps, abnormal skin sensations, stiffness, loss of motor control, weakness, fatigue and sleeping difficulties. Also, patterns of symptom evolution and the order of symptom development were described. Seropositive arthralgia patients described pain as annoying, while RA patients described how the severity of pain intensified before diagnosis, to the point where symptoms were psychologically distressing. Patients with seropositive arthralgia described reddening of the skin and burning sensations which they felt were indicative of the onset of swelling. Intense pain appeared to precede the onset of swelling for those with RA, which was often palindromic and travelled between joints until it later became persistent.

Conclusion: This study highlights the breadth of symptoms that constitute the earliest phases of RA. Further research is needed to develop measures of symptom patterns and clusters to allow the predictive utility of symptoms to be assessed and to allow the integration of aspects of the patient's history into evidence based investigative and management algorithms for use in primary and secondary care.

KEYWORDS

Symptom complex; arthralgia; rheumatoid arthritis; qualitative; early arthritis; symptom experience

INTRODUCTION

Clinically manifest rheumatoid arthritis (RA) is often preceded by a phase of immunological abnormalities and low grade inflammation.[1-3] One of the most specific markers of the disease are antibodies to citrullinated proteins (ACPA), which may be present several years before the first symptoms appear.[1,3] After symptoms appear, it may take weeks, months and sometimes years before arthritis develops [1,4,5] with some patients passing through a phase of unclassified arthritis, before they fulfil the criteria for RA.[6] Recently there has been increased interest in the earliest phases of RA, partly because treatment started rapidly after symptom onset is associated with a better outcome.[7,8] There is a need to better define the earliest phases of RA in order to achieve a better prediction of those who will go on to develop clinically manifest RA and thus might be candidates for trials of preventive therapies. Furthermore, 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.[9,10] Primary care providers also need clearer information about the nature of symptoms at RA onset, as defining the early symptoms of RA is a challenging task.[11,12]

Recently, the European League Against Rheumatism study group for risk factors for RA identified the assessment of symptoms in patients at risk of RA as a research priority.[13] The reporting of symptoms in retrospect by patients with newly diagnosed RA may be influenced by the passing of time and by the fact that they have received a formal diagnosis. On the other hand, reporting of symptoms by symptomatic patients at risk of developing RA on the basis of the presence of systemic immune abnormalities might not be specific enough, since not all such patients will go on to develop RA. Therefore, a combination of the symptom experiences of these two groups of patients would be most informative. A recent systematic review of the qualitative literature surrounding the early RA symptom experience has identified that no such study exists and has highlighted the need for primary qualitative work specifically aimed at identifying the symptoms of RA prior to and coincident with diagnosis.[14]

The aim of this study is to explore symptom complexes at the beginning of RA through qualitative assessment of the experiences of symptomatic at risk individuals with “seropositive arthralgia” and patients newly diagnosed with RA.

METHODS

Qualitative methods, including an active feedback procedure, were used to investigate the views of seropositive arthralgia patients and those newly diagnosed with seropositive RA in Amsterdam, The Netherlands, and Birmingham, UK, respectively. Ethical approval for this study was obtained from the Slotervaart Ethical Committee and the Preston Research Ethics Committee and all patients gave written informed consent.

Participants

Fifteen adults at risk of RA (anti-CCP positive and nearly all with – sometimes intermittent – arthralgia, further referred to as seropositive arthralgia patients) were recruited from an ongoing prospective cohort at the Jan van Breemen Research Institute in Amsterdam, The Netherlands.[4] Eleven adults diagnosed (using the 2010 ACR/EULAR criteria [15]) with sero-positive RA in the past 12 months (referred to as newly diagnosed patients with RA) were recruited from a secondary care early arthritis rheumatology clinic in Birmingham, United Kingdom. Participants were recruited between January and September 2012. Characteristics of participants are presented in **Table 1**.

A total of 119 seropositive arthralgia patients, and 80 newly diagnosed patients with RA were mailed an invitation to participate in a focus group discussion or individual interview, respectively, about their symptom experiences. Main reasons for not participating were difficulties in arranging suitable times and locations for interviews.

Interview procedure

Focus group discussions and semi-structured interviews (here after referred to as interviews) were guided by an interview schedule developed from a literature review and consultation with patient research partners (see table 2)**.** Research Partners primarily suggested additional questions for the schedule. The schedule explored perceptions of symptoms, impact of symptoms and reactions to symptoms, in the context of both past and current symptoms for those at risk of RA, and past symptoms for those who were

newly diagnosed with RA. Interviews were conducted by LvT, RJS and RT and were supported by patient research partners (WH and BM). Interviews lasted approximately 60 to 90 minutes, and were audio-recorded and later transcribed verbatim.

An interactive feedback procedure was used between seropositive arthralgia patients and patients newly diagnosed with RA. This process allowed each group of participants to reflect on the experiences of the other group; for example, the symptom experiences of early RA patients were feedback to seropositive arthralgia patients for discussion and reflection. Similar processes are commonly used to inform assumptions about the validity of qualitative data,[16] however, here an adapted *knowledge translation* process was used to exchange data and perspectives among participants and the research team.[17]

The knowledge translation process began with a summation of the findings collected from the first four interviewees with seropositive arthralgia. The summarised findings were incorporated into the interview scheduled and presented during the first four interviews with newly diagnosed RA patients (see table 2). A summary of the first 4 interviews with RA patients was then fed in to interviews with arthralgia patients. This interactive knowledge translation process took place on two occasions. In addition, the research teams in Amsterdam and Birmingham shared and discussed emerging themes and selected quotations. The emerging themes were added to the original interview schedule (see table 2). Through this process the perceived symptoms of those with seropositive arthralgia were presented to those newly diagnosed with RA. This process was then reversed so the symptom experiences of those newly diagnosed with RA could be fed back to those with seropositive arthralgia.

Analysis procedure

Data were analysed using inductive thematic analysis methods.[18] Data were collected until thematic saturation was reached and it was evident that no new themes were emerging. The transcripts where coded by independent researchers (LvT and MS in Amsterdam, and RJS and RT in Birmingham) using NVivo software for qualitative data analysis.[19] Independently coded transcripts were compared between researchers to develop reliable and inclusive themes. Differences were discussed until consensus was reached. The initial codes were grouped together into the most noteworthy and frequently occurring

categories. During a meeting and teleconferences between researchers (LvT, RJS, LvdS, MS, CM, KR and DvS), the emerging themes were discussed and agreed upon.

RESULTS

The major themes discussed by participants included the symptoms experienced, the pattern of symptoms experienced and the impact of symptoms. Symptoms that were common in patients with seropositive arthralgia and those newly diagnosed with RA are presented and differences are described where applicable. Quotations to support the themes are presented in tables 3-5 (quotes from seropositive arthralgia patients are coded with the prefix 'SA' and those from patients newly diagnosed with RA with the prefix 'RA').

Theme 1: Pain in and around the joints (see table 3)

Both groups described pain as core to their symptom experience, although the descriptions of pain between those who were at risk and those who were newly diagnosed with RA differed in intensity. Seropositive arthralgia patients described pain as bothersome and annoying, primarily because of its impact on sleep and its intermittent nature (SA theme 1, quote 1, further referred to as SA1Q1). Seropositive arthralgia patients suggested that they could feel intermittent episodes of pain "coming on", and that pain would follow exertion or mild injury (such as a knock to the leg – SA1Q2). Patients who were newly diagnosed with RA recalled consistent levels of pain at symptom onset which progressed to more intense levels before RA was diagnosed (RA1Q1 and RA1Q2). The later stages of pain were described as excruciating (RA1Q3).

Seropositive arthralgia patients likened their pain to muscular sensations experienced after intense exercise (SA1Q3), participants used words such as going sour (explanation by the authors: a common Dutch expression for the sensation of muscle pain and stiffness after intense exercise) and burning. When this sensation was described to those newly diagnosed with RA, they recognised this symptom and described their own experiences of muscle fatigue (see theme 4) and muscle cramps (RA1Q4). In addition, newly diagnosed patients described tingling sensations that would come on suddenly, or act as a

"warning" (RA1Q5). Patients newly diagnosed with RA described how tingling sensations preceded a loss of functioning in the joints; for example, one person described that, following tingling sensations, he could no longer use his hands (RA1Q6). Following feedback from patients with RA, tingling was explored with seropositive arthralgia patients, and this symptom was recognised by some, however, the description of tingling was elaborated on and described as "needle pricks" (SA1Q4) and similar to the sensation experienced when one's hands go from cold to hot temperatures very quickly (SA1Q5). A final symptom described by a seropositive arthralgia individual was intense and constant cracking in the feet (SA1Q6), however, when this symptom was fed back to early RA patients this intensity of cracking joints was not experienced.

Theme 2: Joint swelling, warmth and redness around the joints (see table 3)

Some seropositive arthralgia patients experienced transient episodes of joint swelling, with burning sensations, warmth (i.e. joints feeling physically warm to touch) and redness of the skin around their joints (SA2Q1, SA2Q2 and SA2Q3). They suggested that these felt like they could be the onset of inflammation (SA2Q2 and SA2Q3). Following symptom feedback, patients newly diagnosed with RA recalled burning sensations in the joints at symptom onset (RA2Q1 – also see theme 1 for descriptions of burning sensations). Patients newly diagnosed with RA linked the experience of burning sensations to a time preceding the onset of swelling, and suggested that this sensation may have been an indication that swelling was imminent (RA2Q1).

Patients newly diagnosed with RA described the intensity of pain at RA onset, and suggested that swelling occurred later, as the illness progressed (RA2Q2). In addition, it was suggested that the intensity of the swelling did not match that of the pain experienced (RA2Q2 and RA2Q3). When swelling eventually emerged, patients reported transient periods of joint swelling (RA2Q4), and noted that swelling would appear in one location and then move to another joint (RA2Q5). Finally, people with RA noted the symmetrical pattern of swelling (RA2Q6).

Theme 3: Joint stiffness (see table 4)

Seropositive arthralgia patients described feelings of stiffness which lasted longer as their illness progressed (SA3Q1). The sensations which patients in both groups reported that were associated with stiffness included feelings that joints were not lubricated (RA3Q1), numbness (RA3Q2), and the restrictions it placed on movement (SA3Q2). Sometimes morning stiffness was described as painful (RA3Q3), however this was not always the case (RA3Q4). Another feature of stiffness that differed between patients was the time of day this symptom was experienced, with some experiencing morning stiffness upon waking and others experiencing stiffness in the evening.

Theme 4: Weakness and loss of motor control (see table 4)

Weakness, also described as a loss of muscular strength was described by seropositive arthralgia patients (SA4Q1), and interestingly, some seropositive arthralgia patients reported having to use specialist equipment to aid everyday activities including needing a device to open objects such as jars (SA4Q2). Seropositive arthralgia patients and patients who were newly diagnosed with RA both described instances where a complete loss of muscle function occurred which had resulted in falls (RA4Q1) and dropping objects (SA4Q3). Patients described a loss of control (RA4Q2) and being unable to grip and grab objects was a problem (RA4Q3). It was noted that these episodes could occur abruptly and unexpectedly with not obvious precipitant (SA4Q4), but also that loss of strength could follow tingling sensations (RA4Q4 – see theme 1).

Theme 5: Fatigue, sleeping difficulties and depressive symptoms (see table 5)

Fatigue was described by both groups in similar ways. Participants described extreme cases of fatigue which resulted in falling asleep (SA5Q1), and being unable to get up from the floor (SA5Q2). Fatigue was linked to sleeping difficulties in both groups (SA5Q3 and RA5Q1). Participants in both groups described the experience of pain as being a barrier to sleep and quality of rest (SA5Q4 and RA5Q2). A seropositive arthralgia patient felt that severe fatigue was a signal for the onset of other symptoms (SA5Q5), however, following feedback this was not identified, nor reflected in the experiences of patients newly diagnosed with RA.

Participants in both groups described the psychological distress caused by their symptoms. Patients with RA described crying and being in a state of distress (SA5Q6, RA5Q3 and RA5Q4). Also, another patient newly diagnosed with RA suggested that symptoms of depression increased as their illness progressed (RA5Q5). Patients with seropositive arthralgia were also psychologically impacted by the symptoms experienced over the course of their illness , one person described 'wanting out' (SA5Q4).

Not quite fitting in the above themes, two people newly diagnosed with RA described a large amount of weight loss in the 18 months before diagnosis (RA5Q6). However, a loss of weight was not recognised by arthralgia patients.

Theme 6: Pattern of symptom experience and onset (see table 5)

Seropositive arthralgia patients described symptoms which were intermittent and non-persistent, which appeared in this pattern over a number of years (SA6Q1). Patients provided descriptions of palindromic episodes, where symptoms would increase in intensity, remain for a few days, and then resolve (SA6Q2 and SA6Q3). One seropositive arthralgia patient described symptoms slowly becoming more intense (SA6Q5). Patients newly diagnosed with RA described longer periods of time between symptom intensification and resolution (RA6Q1 and RA6Q2). For RA patients the period of time with symptoms they recalled was often weeks or months (as opposed to the time frame of days presented by seropositive arthralgia patients).

Seropositive arthralgia patients and newly diagnosed RA patients reported that symptoms could move from joint to joint (SA6Q4 and RA6Q3), however, in some cases patients were very specific about the location of symptoms, often the hands were discussed (RA6Q4, RA1Q1, RA1Q6 and RA2Q2). In addition other patients remarked on the persistence of symptoms such as pain (RA1Q1) and the eventual constancy of other symptoms such as swelling (RA6Q3).

DISCUSSION

This qualitative exploration of symptoms experienced by patients with seropositive arthralgia and those newly diagnosed with seropositive RA provides an insight into the complexity of disease onset as

experienced by patients themselves. Across themes 1 to 6, patterns of symptom evolution, symptom coexistence and symptom ordering are described and implied. Under theme 1 the evolving intensity of pain between seropositive arthralgia and RA onset was described. Theme 2 described how pain, burning sensations, tingling, warmth and skin reddening may precede the onset of persistent swelling. Theme 3 highlighted that stiffness can be present with or without the sensation of pain. Theme 4 identified a common problem of sudden weakness, and loss of motor control, which in some cases was preceded by flashes of pain and tingling. Theme 5 highlights that fatigue, sleeping difficulties and emotional distress can occur anywhere in the disease cycle, however, weight loss may develop later in the disease course. In addition, this research highlights the importance of assessing the pattern and intensity of symptoms.

This qualitative investigation has furthered our understanding of the symptoms experienced by patients during the earliest phases of RA, and has identified many symptoms not described in a recent literature review of early RA symptoms.[14] Symptoms uniquely identified by this investigation included numbness, restricted movements, loss of strength, sudden loss of function (dropping objects), muscle fatigue, muscle cramps, abnormal skin sensations, weight loss and finally burning sensation, warmth and redness around the joints. In addition this study identified symptoms common to the experience of patients with seropositive arthralgia and those with RA including pain, fatigue, tingling, stiffness, psychological distress and muscle weakness. Other symptoms, such as persistent swelling and weight loss, were experienced primarily by RA patients, suggesting that these symptoms may develop later in the course of disease, nearer to the onset of clinically apparent RA. Burning sensations, warmth and redness of the skin were described by seropositive arthralgia patients, and were suggested to feel like a “pre-swelling state”. This suggestion was endorsed by RA patients who identified with burning sensations, warmth and skin redness and suggested that these did precede swelling during the development of their disease.

By collecting data from seropositive arthralgia and newly diagnosed RA patients we aimed to minimise recall bias and encourage reflectivity. Feedback and knowledge translation techniques were used to allow participants to reflect on the experiences of others, and to prompt recall and disclosure of symptoms

experienced until thematic saturation was reached. A limitation of this study is that many of the symptoms explored were reported retrospectively, with in some cases, a long interval between symptom onset and interview. This was inevitable, as for many patients the symptoms are insidious and RA often does not begin abruptly. Furthermore, it is known that many patients delay for long periods of time before seeking help with symptoms of RA adding to the delay[20]. If only those RA patients with a short window from symptom onset to interview date had been included, this would systematically have excluded those patients with a very particular pattern of onset i.e. the insidious one. Therefore, the broad range of symptom durations in our patients is, in some respects, a strength rather than a weakness as it gives us a broad cross section of RA patients. In combination with the feedback strategy between arthralgia and RA patients we will hopefully have minimised the number of symptoms that RA patients might have forgotten to mention in initial open questioning.

We cannot be certain that patients who declined our invitation for an interview had similar symptoms to patients that participated. The main reasons for not wanting to participate were the inability to find a suitable time, although other factors might have contributed. However, in terms of age and gender, our study population reflects the general RA population. Particular strengths of the study include the involvement of patient partners in the design, data collection and interpretation phase, as well as the exploration of symptoms in two different yet comparable European countries.

There is a large body of evidence showing the importance of early treatment in RA to improve patient outcome and avoid long-term joint damage. To detect RA in its earliest stages, tests for the presence of rheumatoid factor (RF) or ACPA in the blood can be used. However, these are only present in 50-65**%** of patients that will eventually go on to develop RA, and the positive predictive value of these tests in the general population is low.[1] Therefore, testing serology is not always the most appropriate method for assessing the presence of disease. Patients presenting with joint pain are common in primary care settings, and as such general practitioners need decision aids which incorporate clinical symptoms with diagnostic tests to improve the early diagnosis of RA and promote better patient outcomes. The development of a 'symptom questionnaire' to assess the frequency and intensity of symptoms and their evolution in

individuals at risk of RA could be an important aid in identifying patients at risk of RA. Through this approach, refinement of algorithms for use in secondary care to predict RA development in patients with unclassified arthritis [21] and patients with seropositive arthralgia [22] 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.[23] Maximising the benefit from a patient's clinical 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.

KEY MESSAGES

1. Understanding the symptoms that characterise the earliest stages of RA is important if treatment is to be started early.
2. Patients at risk of developing RA and those with early RA experience a broad range of symptoms
3. Symptoms of patients at risk of RA include pain, stiffness, fatigue, burning sensations, loss of motor control, weakness, muscle cramps, sleep disturbance and abnormal skin sensations.

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Table 1: Characteristics of participants

Characteristics	**Arthralgia patients (n=15)**	**Early RA patients (n=11)**
Gender (n)	11 females	8 females
Age range	42 - 77 years	33-90 years
Age mean (SD)	54 (11) years	46 (10) years
Duration from symptom onset to time of interview Median (IQR)	12 (6-18) months	48 (18-50) months

Table 2: Example interview questions and feedback questions

<table>
<tr><td colspan="2">Interview questions (taken from the interview schedule)

Tell me about how your symptoms started?

How have your symptoms progressed?

Can you describe the symptoms that you experience?

When you first developed your symptoms what did you think had caused them?

As your symptoms evolved did your reactions change?

Which symptoms are the worst for you?

How did you react to your initial symptoms of arthritis? (worried, scared)

What happened during the weeks or months before you experienced symptoms?</td></tr>
<tr><td colspan="2">Feedback and knowledge translation

'We are asking these same questions to a second group of people who have not been diagnosed with RA yet, but who are at increased risk of developing RA/ have recently been diagnosed with RA. They describe several symptoms and I would like to hear from you if you recognise these symptoms’</td></tr>
<tr><td>Tingling as a warning

Burning

weakness

Weight loss

Joint pain and swelling

Stiffness

Fatigue and sleep disturbance

Palindromic aspects of onset

Progression of symptoms from one area to another</td><td>Muscular pain, similar to pain after exercise

Loss of strength or feeling weaker than usual

Objects falling from hands

Pain or swelling that appeared and then quickly disappeared

Difficulties bending fingers

Pain which gradually got worse

Experience/hear a “crack” in your joints

Difficulties sleeping

Fatigue preceding flare of other symptoms</td></tr>
</table>

Table 3: Supporting quotations for themes 1 & 2

Quote code	Theme 1: Pain in and around the joints
SA1Q1	"Especially the pain was very annoying, that could sometimes wake me up at night."
SA1Q2	"When you make a misstep or you bumped into something, then I experience the pain starts to come up ... it takes only one day or so and then it decreases again."
SA1Q3	"It's like I have run the marathon, unprepared, twice. Completely turned sour, that feeling, muscles gone sour."
SA1Q4	"Like those little needle pricks ... like those little pricks, it's really weird."
SA1Q5	"Like when your hands have been really cold and it suddenly gets warm."
SA1Q6	"I cannot walk through a space on bare feet without everyone hearing me. Not my foot touching the floor, but 'crack'. Basically the whole day. I can feel that at night too, it is unpleasant."
RA1Q1	"The hand pain was pretty constant practically most of the time ... it was only when I was diagnosed that had actually started to feel pain in the joints."
RA1Q2	"It started on my right hand on my index finger... So initially, I didn't think it was anything strange I just live with it and that was for a few months. And then only about six months later and I started getting pain in my feet in the middle where the ball of the foot is.
RA1Q3	"Because the pain is as chronic, as bad as any pain can get. It would be a bit like having severe toothache or having, like a bad break in your toe or breaking your wrist."
RA1Q4	"It was really hard sometimes, especially if you get muscle cramps"
RA1Q5	"The only warnings you'd get was tingling sensation. That was the only warning you'd get, which obviously scared the life out of me."
RA1Q6	"At first I'd get tingling sensation in my fingers and within an hour couldn't use my hand, for example couldn't turn the key in the ignition of the car, just no power, zero

	pinch grip."
Quote code	**Theme 2: Joint swelling and redness around the joints**
SA2Q1	"You can see it now as well, they are a bit reddish again."
SA2Q2	"It starts slowly. But with red marks, it's not really swollen, but it does feel warm, so it feels like an inflammation."
SA2Q3	"It's a kind of burning, like it will be inflamed. I have that regularly, once every two or three weeks. It feels warm, but not painful or anything."
RA2Q1	"Like a burning ... that there is something there, like I got burnt from inside, like that when it, I feel, you know, then I got a swelling there, I feel there is something fire in my fingers."
RA2Q2	"If you looked at my hand last year there was no swelling really of any significance, but the pain underneath was drastic. Considering how bad the pain was I would have expected my fingers to be huge."
RA2Q3	"Pain was worst, swelling was hardly noticeable."
RA2Q4	"It was the pain and the swelling usually would go down it would come up for a few weeks and then go back down."
RA2Q5	"I had pain sometimes in my knee, sometimes in my feet, sometimes in my ankles yes. And also swelling as well."
RA2 Q6	"It was like puffy, but because it was both hands we were like hang on a minute this is not an insect bite there's some symmetry in this.'

Table 4: Supporting quotations for themes 3 & 4

Quote code	Theme 3: Joint stiffness
SA3Q1	"Every morning. I wake up, and it is stiff. It is in fact worse now than a month ago. The stiffness lasts longer than before. It takes a few minutes …"
SA3Q2	"It's not a matter of a few minutes for me. No, it takes much longer, about 20 minutes. But the difference could be, that I have a lot of complaints in my feet. So for me, getting up in the morning is already a hurdle because of the pain in my feet. My hands are stiff as well, but that is solved faster, because you use your hands more."
RA3Q1	"It's like it hurts but it would be like, just not like lubricated."
RA3Q2	"It feels like when you lie on your head and you get like a stiff neck ... it felt just like that, but it is the same sort of numbness and sheer pain if you try and move round or look round, it is that sort of pain, it's quite disabling like."
RA3Q3	"The early morning as well. So stiff, the fingers are so stiff. In the morning ... and in the evening when it is getting about 6 or 6.30 you know I start feeling that there is stiffness in the fingers and pain as well."
RA3Q4	"There wasn't any pain involved I do remember waking up with my hands in like a claw position, and they were stiff, and it took about 15 minutes just to loosen up, and then get out of bed. And there wasn't any pain ..."
Quote code	**Theme 4: Weakness and loss of motor control**
SA4Q1	"I am much less strong than I used to be, I was really strong ... Then you think, what a weakness."
SA4Q2	"The loss of strength is something I notice as well. I adjusted everything at home, you know, equipment to open things …"
SA4Q3	"I'm standing with a bucket of hot water and suddenly let it fall out of my hands. I was so ashamed. But I have the same with a cup of tea, I'm talking and the next thing I know, it falls out of my hands."

SA4Q4	"One moment I have it in my hands and the next moment it is down on the table. And don't ask me how; it's not like there is a pain flash or anything. It's like, at that moment my finger says: 'not now please'."
RA4Q1	"I'd get up in the morning to walk and I'd just go to the floor, was nothing there."
RA4Q2	"It's out of your control, completely out of your control."
RA4Q3	"But if you still get full power of your hands you can grip things perfectly ... once it moves to there [pointing to wrist] you lose all control of your hands from there downwards, you can't grip, you can't grab anything."
RA4Q4	"Everything is fine and within two hours of working 'oh no, tingling sensation in my hands' I'll call my boss over "I can't use my hands."

Table 5: Supporting quotations for themes 5 and 6

Quote code	Theme 5: Fatigue, sleeping difficulties and depressive symptoms
SA5Q1	"That fatigue; like I'm sitting in the couch ready to watch some TV and then I get so fatigued that I completely doze off, really extreme."
SA5Q2	"If I would fall now, I will just remain lying down, doesn't matter where I am. It's really extreme fatigue, not just a little tired."
SA5Q3	"Sometimes I wake up fatigued, I think I didn't sleep well that night."
SA5Q4	"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."
SA5Q5	"First, I get very tired…really extremely tired and then some time later, my wrist starts…and then I think "oh yeah that's why the fatigue, that was it". For me, it really starts with extreme fatigue."
SA5Q6	"You are not able to do anything, it really hurts. The tears are on my cheeks."
RA5Q1	"I remember that you were in a lot of pain generally not being able to get comfortable and not being able to sleep because of pain."
RA5Q2	"If you turn over in bed ... it's like, it's like you are breaking every bone in your body."
RA5Q3	"When I was so that bad, you know, swollen hands also up to here ... And I was crying just like a baby you know."
RA5Q4	"Oh naturally I am crying with the pain."
RA5Q5	"I think the fact that you can get rather depressed after a time with it, you have to try and shake yourself out and it isn't always easy."
RA5Q6	"I lost 2 ½ stones in the 18 months before diagnosis and I didn't know why I was losing weight, I went from 17 ½ stones to 15 stones. I couldn't explain it."
Quote code	**Theme 6: Pattern of symptom experience and onset**

SA6Q1	“In these two and a half years I have had phases of ups and downs.”
SA6Q2	“Then I experience the pain starts to come up and then I recognize it, it takes only one day or so and then is decreases again.”
SA6Q3	“It stays for 3 days only and at night it is the worst and that was not pleasant.”
SA6Q4	“I have it mainly in my hands and it ‘jumps’ quite often, then at the left side, then at the right side, then my wrist, then my elbow, then again my shoulder.”
SA6Q5	“Yes, slowly, it’s like turning on the radio. You slowly turn on the radio, and it gets more intense so to speak.”
RA6Q1	“It stopped for seven months and I had no symptoms whatsoever and then it started again. When it started again, it came back with vengeance, flashing lights and all.”
RA6Q2	“It was the pain and the swelling usually would go down it would come up for a few weeks and then go back down and I be alright then but this time it didn’t go down it was just constantly swollen.”
RA6Q3	“It don’t stick, it don’t stay anywhere.”
RA6Q4	“My hands have been a problem most of the time, particularly in my thumbs that was where it all started.”