Concise report

Fibromyalgic rheumatoid arthritis and disease assessment

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Abstract

Objective. We evaluated fibromyalgic RA to determine its clinical impact, identification using core clinical assessments and influence identifying active disease using disease activity scores (DAS-28).

Methods. We examined the impact and identification using core clinical assessments (tender minus swollen joint counts) of fibromyalgic RA (≥11 tender points) in initial (105 patients) and replicate (100 patients) cohorts. Receiver operator characteristic (ROC) curves optimized the cut-off points using tender minus swollen joint counts; their validity was confirmed in a routine practice cohort (321 patients). We evaluated whether fibromyalgic RA affected the identification of active disease using DAS-28 (≥5.1) and the clinical disease activity index (CDAI).

Results. A total of 18/105 and 12/100 patients in initial and replicate cohorts, respectively, had fibromyalgic RA. This was identified by ≥7 tender minus swollen joint counts with 83% sensitivity and 80% specificity in the initial cohort (72 and 98% in replicate, respectively) and ROC area under the curve 0.80 (0.94 in replicate). “Fibromyalgic” RA (tender point scores in initial and tender minus swollen joints in clinical practice cohorts) had higher DAS-28, pain, fatigue and HAQ scores. More fibromyalgic RA patients had active disease by DAS-28 (odds ratio 14.3; 95% CI 5.5, 37.1; and CDAI 17.2; 95% CI 6.1, 48.5); conventional assessments (three or more tender joints; three or more swollen joints; ESR ≥28 mm/h) showed no difference (1.75; 95% CI 0.72, 4.3).

Conclusion. Fibromyalgic RA affects 12–17% of RA outpatients and results in worse functional outcomes. DAS-28 scores over-interpret active disease in fibromyalgic RA.

Key words: Rheumatoid arthritis, DAS-28, Tender points, Fatigue.

Introduction

RA spans several distinct clinical phenotypes. One of these includes co-existing fibromyalgic features; this phenotype has been termed “fibromyalgic RA” [1]. Its importance has been highlighted by Wolfe and colleagues [2, 3] who described its characteristic high levels of pain, fatigue and disability. An estimated 10–20% of RA patients have fibromyalgic RA.

The high pain and disability scores seen in fibromyalgic RA suggest that these patients will also have high scores using summative assessments like the disease activity score (DAS). This perception is supported by previous research that shows that DAS scores are often high in patients with fibromyalgia without RA [4]. DAS scores are particularly important in treatment decisions about DMARDs and biologics [5, 6]. If DAS scores are disproportionately high in relation to the level of inflammatory synovitis in fibromyalgic RA, the value of DAS assessments in these patients is open to question. This is a particularly cogent issue as a recent study of fibromyalgic RA by Coury et al. [7] suggested that DAS-28 over-estimated disease activity in these patients.

We have studied patients with fibromyalgic RA with three aims. First, we confirmed that its prevalence and clinical impact in UK patients with RA reflects experience in other countries. Secondly, we determined whether the
conventional core data set of clinical assessments in RA can be used to identify patients with fibromyalgic RA. Finally we examined the influence of fibromyalgic RA on the identification of active disease using DAS-28 scores and ascertained the limitations of DAS-28 in this setting.

Methods

Defining fibromyalgic RA

Patients with RA invariably have pain from all four limbs and their spine. Consequently, in applying the ACR criteria for fibromyalgia [8] we took the presence of $\geq 11$ tender points as the key diagnostic criterion to identify fibromyalgic RA.

As tender point counts are not usually undertaken in RA patients, we examined the possibility of using high tender joint counts as a surrogate for higher tender point counts. We corrected for the activity of synovitis by subtracting the number of swollen joints; we considered using an alternative correction such as dividing by the number of swollen joints but as this would mean dividing by zero in some patients such a method was not practical.

Patients

Initial cohort. A cross-sectional study enrolled 105 consecutive RA patients attending routine outpatient clinics who met the ACR criteria. They comprised 80 females and 25 males of mean age 60 years (range 24–88 years); 70% were seropositive for RF.

Replicate cohort. A second cross-sectional study enrolled 100 similarly selected RA patients. They comprised 77 females and 23 males of mean age 62 years (range 25–86 years); 65% were seropositive for RF.

Routine practice cohort. A previous cross-sectional study enrolled 321 similarly selected RA patients in which core data set assessments had been made. They comprised 246 females and 75 males of mean age 60 years (range 23–87 years); 81% were seropositive for RF.

Ethical approval and informed patient consent was obtained for this study. The King’s College Hospital Ethics Committee approved the study.

Assessment of tender points, pain and fatigue

Fibromyalgic tender point assessment used methods recommended for diagnosing fibromyalgia. Pain was measured using a 100-mm visual analogue scale (VAS). Fatigue was measured using a double-anchored 100-mm VAS.

Other assessments

Demographic data (age, disease duration, sex and ethnic origin), physician global assessment, early morning stiffness and DAS-28 and its constituents (patient global assessment, 28 tender and swollen joint counts and ESR), the clinical disease activity index (CDAI) [9] and the HAQ were also recorded.

Analysis

All analyses used the Statistical Package for the Social Sciences (SPSS® 14.0 for Windows). Group data were reported using means (S.D.) and ranges. To determine if tender minus swollen joint counts could identify fibromyalgic RA as accurately as tender points, receiver operator characteristic (ROC) analysis was employed. We compared subgroups using Student’s t-test and frequencies using the odds ratio (OR).

Results

Prevalence of fibromyalgic RA

A total of 18/105 (17%) patients in the initial cohort and 12/100 (12%) patients in the replicate cohort had $\geq 11$ tender points and met the criteria for fibromyalgic RA.

Identifying fibromyalgic RA using tender joint counts

In the initial cohort, tender point counts correlated strongly with tender joint counts (Pearson’s correlation $r = 0.74$) and tender minus swollen joints ($r = 0.70$); tender divided by swollen joints could not be used as it would mean dividing by zero in patients with no swollen joints. To take into account patients with very active synovitis having high numbers of both tender and swollen joints, we elected to evaluate tender minus swollen joints in more detail.

ROC analysis showed that the area under the curve using tender minus swollen joints to identify fibromyalgic RA patients defined by tender point count score was 0.86. Tender minus swollen joint counts of $\geq 7$ predicted the presence of $\geq 11$ tender points with 83% sensitivity and 80% specificity.

In the replicate cohort, tender point counts correlated with tender joint counts ($r = 0.78$) and tender–swollen joint counts ($r = 0.77$ in both cases). ROC analysis showed that the area under the curve using tender minus swollen joints to identify fibromyalgic RA patients defined by tender point count score was 0.94. Tender minus swollen joint counts of $\geq 7$ predicted the presence of $\geq 11$ tender points with 72% sensitivity and 98% specificity.

Clinical impact of fibromyalgic RA

Patients with fibromyalgic RA identified by high tender point scores (initial cohort) or high tender minus swollen joint counts (initial cohort and clinical practice cohort) had higher tender joint counts, patient global assessments, DAS-28 scores, pain scores, fatigue and HAQ (Table 1). However, their swollen joint counts were similar to those of other RA patients.

Impact of fibromyalgic RA on the definition of active disease

The impact of fibromyalgic RA, assessed by tender point counts of $\geq 11$ on the definition of active disease was evaluated by combining data from the initial and replicated cohorts.
Most patients with fibromyalgic RA had DAS-28 ≤5.1 (79%) compared with only a minority of other patients (20%); the OR and 95% CIs for having active disease by DAS-28 criteria with fibromyalgic RA compared with RA without fibromyalgia was 14.3 (95% CI 5.5, 37.1). The same situation occurred if the DAS-28 was replaced by CDAI, taking 22 or more as being active disease with fibromyalgic RA patients having an increased likelihood of being classified as active (OR 17.2; 95% CI 6.1, 48.5).

In contrast, using more conventional assessments based on reaching pre-defined numbers of tender and swollen joints and a high ESR showed that only a minority of patients with fibromyalgic RA had active disease. Using three or more tender and swollen joints and an ESR ≥28 showed that only 29% of these patients had active RA compared with 19% of patients with RA without fibromyalgia. The frequency of active RA defined by these criteria with and without fibromyalgic RA was not significantly increased, with OR 1.75 (95% CI 0.72, 4.3). This difference is shown in Fig. 1. There were similar findings with six or more tender and swollen joints and an ESR ≥28 (OR 2.6; 95% CI 0.88, 7.6).

**Discussion**

Our findings confirm previous reports that 10–20% of RA patients attending specialist units have fibromyalgic RA. All centres evaluating fibromyalgic RA report similar frequencies in patients attending specialist centres. Bliddal and Danneskiold-Samsøe [10] have highlighted the importance of chronic widespread pain in rheumatic diseases including RA, pointing out that not all patients meet accepted diagnostic tender point criteria of ≥11 for diagnosing fibromyalgia. Recent work from Ranzolin et al. [11] also showed that high DAS-28 scores are common in patients with fibromyalgia and RA, and Wolfe [12] suggested the term ‘fibromyalgianess’ applied to such patients whom he considered to have polysymptomatic distress. The balance of evidence suggests that there is a subset of RA patients with a fibromyalgic phenotype who have high pain levels unrelated to synovial inflammation, high fatigue scores and more disability with high HAQ scores. In other rheumatic diseases, particularly connective tissue disorders such as SLE, some studies report limited evidence of an increase in fibromyalgic symptoms [13, 14] whereas other studies show that fibromyalgic features are commonplace [15, 16].

We have shown that conventional core data set measures can be used to identify patients with fibromyalgic RA. Such patients have disproportionately high tender joint counts, and can readily be identified by examining tender minus swollen joint counts. Recent research from Wolfe and Michaud [17] suggests that fibromyalgia and by implication fibromyalgic RA are one end of a spectrum. Consequently using cut-off points of ≥11 tender points or tender minus swollen joint count of ≥7 over simplifies a complex situation. One crucial question is whether it is appropriate to divide patients into those with or without fibromyalgic RA—the evidence suggests that it is better to

**Table 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initial cohort</th>
<th>Routine practice cohort</th>
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<tbody>
<tr>
<td>Tender joints</td>
<td>17 (14, 21)</td>
<td>18 (16, 19)</td>
</tr>
<tr>
<td>Swollen joints</td>
<td>4 (2, 6)</td>
<td>4 (3, 5)</td>
</tr>
<tr>
<td>ESR</td>
<td>65 (49, 69)</td>
<td>65 (49, 69)</td>
</tr>
<tr>
<td>HAQ</td>
<td>2.0 (1.8, 2.3)</td>
<td>2.0 (1.8, 2.3)</td>
</tr>
</tbody>
</table>

Initial and routine practice cohort patients included separately. The ranges of each variable in the study are indicated. Data indicated are mean values (95% CIs).
consider fibromyalgic features as a continuum rather than a diagnosis that is either present or absent. A second related question is whether in this context fibromyalgia is a separate associated disease or a symptom complex; we favour the latter approach. However, irrespective of these questions, we consider that patients with high tender joint counts but few swollen joints differ from the majority of patients with relatively equal numbers of tender and swollen joints. Such patients with a pattern of fibromyalgic RA may need a different approach to symptom control and may require a greater emphasis on exercise and psychological treatment and less emphasis on DMARDs alone.

Using DAS-28 \( \geq 5.1 \) to define active RA has the benefits of simplicity and reproducibility. However, our results show that it may overestimate the activity of patients with fibromyalgic RA. Using CDAI as an alternative to DAS-28 does not change this over-representation. The explanation for this effect is the way in which these indices handle joint counts with equal weighting given to the numbers of tender joints no matter how high these are. The classic entry criteria for trials involve patients having high swollen joint counts [18] and therefore avoid entering patients with a purely fibromyalgic pattern of disease. Our results suggest that there are strong arguments in favour of using conventional trial entry criteria, such as having three or more tender and swollen joints and an elevated ESR, rather than only concentrating on DAS-28 scores.

We appreciate that some patients with many tender points and high tender joint counts who have features of fibromyalgic RA and DAS-28 \( \geq 5.1 \) also have evidence of synovial inflammation with high swollen joint counts. Assessing disease activity in fibromyalgic RA is clearly challenging and complex [19]. However, we consider that using DAS-28 \( \geq 5.1 \) as the sole criterion to define active RA is too simple and will misclassify a substantial number of patients. Such summary measurements need to be tempered with additional clinical assessments to enable patients to receive the optimal treatment they need [20].

**Rheumatology key messages**

- DAS-28 may overestimate the disease activity in patients with fibromyalgic RA.
- Fibromyalgic RA patients can be identified by examining tender minus swollen joint counts.

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**References**


