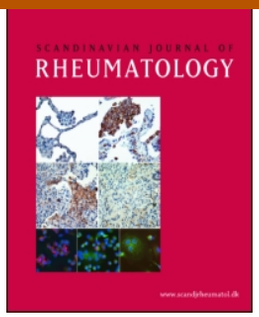

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Contribution of tenosynovitis of small joints to the symptom morning stiffness in patients presenting with undifferentiated and rheumatoid arthritis

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Objective: Morning stiffness (MS) is characteristic of rheumatoid arthritis (RA). Despite its association with functional disability, the extent to which local inflammatory processes contribute to this symptom is unknown. Magnetic resonance imaging (MRI)-detected tenosynovitis of small joints is recognized as an early feature of RA, which is also associated with functional impairments. It has been proposed that tenosynovitis contributes to MS. Therefore, we assessed the relationship between MS and MRI-detected inflammation, in particular tenosynovitis.
Method: In total, 286 consecutive patients newly presenting with undifferentiated arthritis and RA underwent contrast-enhanced 1.5 T MRI of (2–5) metacarpophalangeal, wrist, and (1–5) metatarsophalangeal joints. Scans were scored for tenosynovitis according to Haavardsholm, and for synovitis by Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS). MS was dichotomized as ≥ 60 min or not. Associations between MS and tenosynovitis/synovitis were tested with logistic regression, data were categorized (solitary or simultaneous presence of synovitis/tenosynovitis), and the presence of an additive interaction was assessed.
Results: MS was present in 40% of patients. Tenosynovitis was more often present in patients with MS than without MS [80% vs 65%, odds ratio (OR) 2.11, 95% confidence interval (1.21;3.69)]. Synovitis was more often present in patients with MS [58% vs 44%, OR 1.79 (1.11;2.91)]. In categorized analyses, concurrent synovitis and tenosynovitis had the largest association [OR 2.43 (1.30;4.54)], in contrast to solitary synovitis [OR 0.85 (0.21;3.47)]. The additive interaction was non-significant. The variance explained in all analyses was small (range 4–5%).
Conclusion: Tenosynovitis, combined with synovitis, at small joints is associated with MS and contributes to the pathophysiology of MS.

Morning stiffness (MS) is characteristic of rheumatoid arthritis (RA) and prevalent in 40–50% of patients (1). MS has been a component of classification and remission criteria for RA, illustrating that it is considered a key symptom. Its presence contributes to patients' perceived disease burden as it is consistently associated with functional disability (1–3). Although MS is prevalent and causes functional limitations, its pathophysiology is still poorly understood (1).

It is presumed that both systemic and local inflammation underlie MS (4). Most studies have focused on systemic factors, which is intuitive as the circadian rhythm of symptoms parallels late-night and early-morning rises of pro-inflammatory markers (5). The time relationship and the observation that MS could be relieved by the application of low-dose prednisone during the night makes it likely that systemic inflammatory markers contribute to MS (6).

MS is generally most pronounced in the hands. It is not known which structures are involved: joints or tendons.

However, in proportion to the number of studies focusing on systemic markers, the association with local inflammation is less well studied. An association with swollen joints has been described (1), and some studies showed correlations with ultrasound-detected synovitis (3, 7–9).

More recently, it has been shown that, next to synovitis, tenosynovitis of small joints is characteristic of RA. Tenosynovitis is associated with functional limitations in patients with early inflammatory arthritis (10). In this light, it has been suggested that tenosynovitis contributes directly to MS (11). Some suggestive evidence was obtained but analyses included small patient populations, and other features of local inflammation, such as concomitant synovitis, were not considered.

The fact that MS is a hallmark symptom of RA, but we do not fully understand its pathophysiology, prompted us to

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perform this large cross-sectional magnetic resonance imaging (MRI) study in which we aimed to determine whether tenosynovitis, also in relation to synovitis, at small joints is associated with MS in patients presenting with undifferentiated arthritis (UA) and RA.

Method

Patient population

We studied cross-sectional data of 286 consecutive patients from the Leiden Early Arthritis Clinic (EAC) cohort included between June 2013 and February 2016. The EAC is a population-based inception cohort of patients with recent-onset arthritis and symptom duration < 2 years, as described previously (12). Patients, diagnosed with RA (2010 or 1987 criteria) or UA (not fulfilling these criteria, and no other diagnosis) who underwent baseline gadolinium-enhanced MRI were selected (Supplementary figure S1). The clinical diagnosis was made by the treating rheumatologist. RA was further verified by the patient fulfilling the classification criteria during the first year. Patients with missing MRI scans were excluded (n = 65); they were not different from included patients (Supplementary table S1).

Baseline questionnaires, swollen joint count including 66 joints (SJC66) and tender joint count including 68 joints (TJC68), and laboratory investigations were performed. Written informed consent was obtained from all patients. The study was approved by the local Medical Ethics Committee Leiden (approval number P17.261).

MS measurements

Two questions on MS were answered. The first concerned the presence of MS ('joints stiff in the morning: yes/no') and the second its duration ('stiffness of the joints < 30 min; 30–60 min; 1–2 h; 2–4 h; whole day'). Scores were dichotomized for the presence (≥ 60 min) and absence of MS (either 'no' or duration < 60 min), because this cut-off has been shown to be sensitive and specific for RA (12). In addition, we explored a cut-off of ≥ 30 min (12).

MRI scanning and scoring

Baseline 1.5 T MRI scans were performed (before the initiation of any disease-modifying anti-rheumatic drugs), of metacarpophalangeal (MCP 2–5), wrist, and metatarsophalangeal (MTP 1–5) joints of the more affected side (or the dominant side in case of equal symptoms). Non-steroidal anti-inflammatory drugs were stopped 24 h before MRI. Scans were performed between 09:00 and 16:00 h and scored in line with the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT)–Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) method by two independent readers; the mean scores of both readers were calculated. Semi-quantitative scores ranged from 0 to 3 per location and were summed for total synovitis and tenosynovitis scores. MRI scans were considered positive for MRI-detected tenosynovitis/synovitis if this was present in at least one joint, which was present in < 5% of age-matched healthy controls (described in Supplementary methods).

Statistics

Associations between MS and MRI-detected synovitis/tenosynovitis were tested with logistic regression (MS entered as the dependent variable, and clinical and imaging findings as independent variables). The explained variance was assessed by the Nagelkerke R^2. As synovitis and tenosynovitis often co-occur, to prevent collinearity, we did not perform multivariable analyses but examined associations of isolated and simultaneous presence of synovitis and tenosynovitis by categorizing data. An additive interaction

Table 1. Baseline characteristics of rheumatoid arthritis and undifferentiated arthritis patients, and odds ratios with morning stiffness (MS).

	All patients (n = 286)	MS present (n = 113)	MS absent (n = 173)	OR (95% CI)
Age (years), mean ± sd	57 ± 16	56 ± 15	57 ± 15	0.99 (0.98;1.01)
Female, n (%)	178 (62)	65 (58)	113 (65)	1.39 (0.86;2.26)
SJC66, median (IQR)	3 (1–8)	6 (1–6)	2 (1–6)	1.08 (1.03;1.13)
Symptom duration (weeks), median (IQR)	10 (5–27)	9 (4–27)	11 (5–27)	1.00 (0.99;1.01)
CRP increased (≥ 5 mg/L), n (%)	165 (58)	76 (52)	89 (52)	1.95 (1.18;3.20)
RF positive (≥ 3.5 IU/mL), n (%)	104 (37)	47 (33)	57 (33)	1.36 (0.88;2.12)
ACPA positive (≥ 7 U/mL), n (%)	77 (27)	33 (26)	44 (26)	1.22 (0.72;2.08)

SJC66, swollen joint count including 66 joints; symptom duration: time since the start of any arthritis-related symptoms; CRP, C-reactive protein (positive if ≥ 5 mg/L); RF, immunoglobulin M-rheumatoid factor (positive if ≥ 3.5 IU/mL); ACPA, anti-citrullinated peptide antibody (anti-CCP2; EliA CCP, Phadia, the Netherlands; positive if ≥ 7 U/mL); sd, standard deviation; IQR, interquartile range; CI, confidence interval.
Positive associations with MS were found for CRP positivity; OR 1.95 indicates that patients with an increased CRP had a 1.95 higher odds of having MS than patients with a normal CRP; for SJC66, 1.08 means that per increase in swollen joint the patient had a 1.08 higher odds of MS.

was examined (13) by the relative risk excess (RERI), synergy index (SI), and attributive proportion (AP). In the absence of an interaction, RERI and AP equal 0, and SI equals 1 (13), as described in Supplementary methods.

Sensitivity analyses were performed, first in RA patients (excluding UA patients) and secondly for MS duration ≥ 30 min. Thirdly, as MS is often experienced in the hands, MRI-detected inflammation was assessed in the hand joints (excluding MTP joints).

IBM SPSS version 23 was used, and p values < 0.05 were considered significant.

Results

Patient characteristics

Baseline characteristics are shown in Table 1. Forty per cent of patients experienced MS. They had higher SJC66 and CRP than those without MS (Table 1).

Associations between tenosynovitis and synovitis and MS

The median tenosynovitis score was 7 in patients with and 3 in patients without MS (p = 0.001). The median score for synovitis was 5 in patients with and 3 in patients without MS (p = 0.001) (Figure 1A).

Tenosynovitis was present in 70%, and more often in patients with MS [80% vs 65%; odds ratio (OR) 2.11, 95% confidence interval (CI) (1.21;3.68)]. Synovitis was present in 49%, and more often in patients with MS [58% vs 44%; OR 1.79 (1.11;2.91)] (Table 2).

The explained variance (R^2) ranged between 4 and 5% (Table 2).

Assessment of interaction of concurrent tenosynovitis and synovitis in categorized data

Synovitis and tenosynovitis often occurred simultaneously: combined synovitis and tenosynovitis was present in 127 patients (45%), solitary tenosynovitis in 72 (25%), solitary synovitis in 12 (4%), and 71 (25%) patients had no synovitis or tenosynovitis in the imaged joints. The presence of simultaneous synovitis/tenosynovitis had the strongest association with MS [OR 2.43 (1.30;4.54)], while synovitis without tenosynovitis was not associated in categorized analyses [OR 0.85 (0.21;3.47)] (Table 2, Figure 1B).

The presence of an additive interaction between synovitis and tenosynovitis was explored; although the

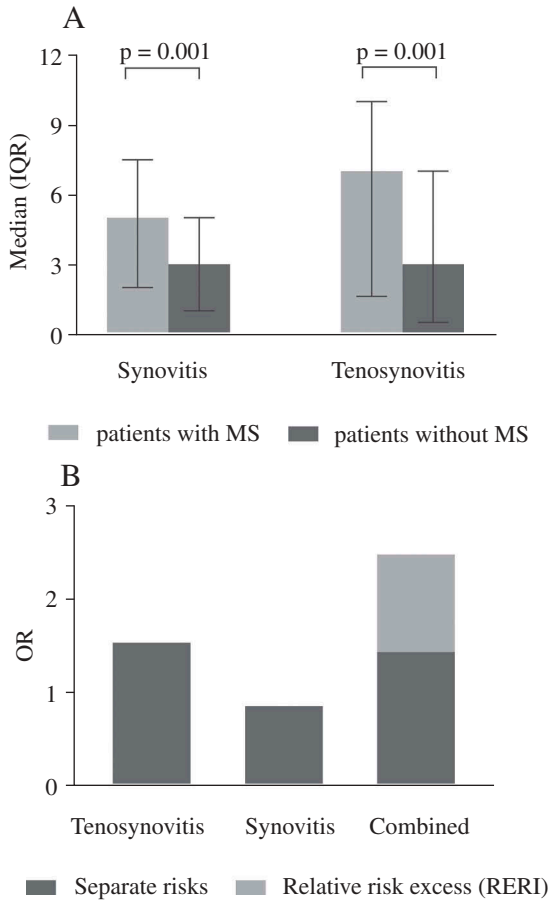

Figure 1. (A) Association of morning stiffness (MS) with magnetic resonance imaging-detected tenosynovitis and synovitis scores in patients with and without MS: median [interquartile range (IQR)]; (B) evaluation of the additive effect of the combined presence of synovitis and tenosynovitis. The relative risk excess (RERI) was 1.05 (–0.52;2.62), attributive proportion (AP) 0.43 (–0.18;1.05), and synergy index (SI) 3.78 (0.05;270.0). OR: odds ratio.

Table 2. Associations of morning stiffness with presence of magnetic resonance imaging-detected tenosynovitis and synovitis, and categorized analyses.

Presence of feature		OR (95% CI)	R^2
	Synovitis	1.79 (1.11;2.91)	0.04
	Tenosynovitis	2.11 (1.21;3.68)	0.04
Categorized features			
Synovitis	Tenosynovitis	OR (95% CI)	
–	–	1.0 (ref.)	0.05
+	–	0.85 (0.21;3.47)	
–	+	1.53 (0.76;3.09)	
+	+	2.43 (1.30;4.54)	

OR, odds ratio; CI, confidence interval.

largest effect was obtained for concomitant synovitis/tenosynovitis, the RERI was 1.05 (–0.52;2.62), AP 0.43 (–0.18;1.05), and SI 3.78 (0.05;270.0), suggesting a small, non-significant additive effect of combined synovitis/tenosynovitis (Table 2, Figure 1B).

Sensitivity analyses

Analyses in RA patients (n = 168) (Supplementary table S2) showed similar results for tenosynovitis and synovitis with MS [OR 1.82 (0.75;4.42)] (Supplementary table S3).

Analyses of MS ≥ 30 min were also similar. The simultaneous presence of tenosynovitis/synovitis was associated with MS [OR 2.65 (1.45;4.84)] (Supplementary table S4 and S5).

Discussion

This cross-sectional study provided evidence for the relationship between MRI-detected tenosynovitis and MS in RA and UA. The largest effect was obtained for simultaneous tenosynovitis/synovitis, while the solitary presence of synovitis was not associated with MS. Importantly, all effect sizes were relatively small and the proportion of variance of MS explained by tenosynovitis was minor. This suggests that local inflammation contributed to a small extent, and implies that other factors may make a greater contribution to the symptomatology of MS.

Most previous studies investigating associations between inflammation and MS focused on systemic inflammatory markers such as cytokines. Very few studies addressed the issue of local inflammation. One study related MS to SJC (1), and a few to ultrasound-detected synovitis (3, 7–9). Our results on SJC were concordant with these studies (1, 2). For example, an OR of 1.05 for MS with SJC was reported (1), which was 1.08 here. To the best of our knowledge, this was the first study to examine the effect of MRI-detected tenosynovitis in relation to MS, while also taking simultaneous presence of synovitis into account. The association between MRI-detected inflammation and MS was similar in RA and the total group.

Previous studies have shown that a duration of MS > 60 min was specific for RA but > 30 min also had good sensitivity and specificity (12). In our data, findings were similar for both durations.

This study had some limitations. First, a uniformly accepted definition of MS does not exist. We collected data on MS duration but not on MS severity. Previous reviews concluded that there is insufficient evidence to prioritize a measure for MS (4, 14). Whether the association of MRI-detected inflammation with MS severity is stronger than that of MS presence is a subject for further studies. Secondly, MRI scans were performed at any time during the day. Ideally, they would have been performed in the early morning, when MS is most severe, but this was not feasible. Previous data showed that MRI-detected inflammation does not change during the day (15), but we cannot rule out that this has resulted in underestimated effect sizes.

The biological mechanisms underlying MS are still poorly understood. An association with local inflammation is presumable since (infiltrated) immune cells, and also fibroblast-like synoviocytes that are resident in the joint at the synovium and in the surrounding synovial compartment, follow the circadian rhythm. As synovitis and tenosynovitis often occur simultaneously, we hypothesized that this co-occurrence may contribute to MS. Indeed, we observed the highest association for simultaneous synovitis/tenosynovitis. However, we found no additive interaction in relation to MS. Thus, concomitant synovitis/tenosynovitis had the strongest association with MS, without an additional effect.

Conclusion

The simultaneous presence of tenosynovitis and synovitis was particularly associated with MS. However, the effect sizes and percentages of the explained variance suggested that the contribution of local inflammation to this symptom, as detected by MRI, is rather limited.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Supporting information

Additional Supporting Information may be found in the online version of this article.

Supplementary figure S1. Flowchart of the patient selection.
Supplementary table S1. Baseline characteristics of patients with and without an available MRI.
Supplementary table S2. Sensitivity analyses: baseline characteristics of patients with RA and odds ratios for presence of morning stiffness.
Supplementary table S3. Sensitivity analyses in patients with RA for odds ratios for presence of morning stiffness and categorized analyses.
Supplementary table S4. Sensitivity analyses for when MS was defined as a duration > 30 minutes; odds ratios and categorized analyses.
Supplementary table S5. Sensitivity analyses for odds ratios for presence of morning stiffness with MRI-detected synovitis and tenosynovitis in MCP and wrist joints and categorized analyses.
Supplementary methods. MRI protocol; MRI scoring and dichotomizing; MR readers; Calculations for assessment of the presence of a biologic interaction; and References

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