Clinically suspect arthralgia and early rheumatoid arthritis: advances in imaging and impact on daily life

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The contribution of tenosynovitis of small joints to the symptom morning stiffness in patients presenting with Undifferentiated and Rheumatoid Arthritis

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Abstract

Objective

Morning stiffness (MS) is characteristic of Rheumatoid Arthritis (RA). Despite its association with functional disability, it is insufficiently known to what extent local inflammatory processes contribute to this symptom. MRI-detected tenosynovitis of small joints is increasingly recognized as an early feature of RA, which also associates with functional impairments. Recently it was proposed that tenosynovitis may contribute to MS. Therefore, we assessed the relationship between MS and MRI-detected inflammation and in particular tenosynovitis.

Methods

286 consecutive patients newly presenting with undifferentiated arthritis and RA underwent contrast-enhanced 1.5T MRI of (2-5)MCP-, wrist- and (1-5)MTP-joints. Scans were scored for tenosynovitis according to Haavardsholm and for synovitis, conform the RAMRIS-method. MS was dichotomized as >60 minutes 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% versus 65%), OR 2.11 (95%CI 1.21; 3.69). Also synovitis was more often present in patients with MS (58% versus 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 the sole presence of synovitis (OR 0.85 (0.21; 3.47). The additive interaction was non-significant. The variance explained in all analyses was small, ranging 4-5%.

Conclusion

Tenosynovitis, combined with synovitis, at small joints associated with MS and contributes to the pathophysiology of MS.

Introduction

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 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 inflammation and local inflammation underlie MS.[4] Most studies focussed 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. Therefore it is presumable that next to systemic inflammation, also local inflammation is important for the occurrence of MS. However, in proportion to the number of studies focussing 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]

Recently, it has been shown that, next to synovitis, tenosynovitis of small-joints is characteristic of RA . Tenosynovitis 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, like concomitant synovitis, were not considered.

The fact that MS is a hallmark symptom of RA of which we do not fully understand the pathophysiology prompted us to perform this large cross-sectional MRI-study in which we aimed to determine if tenosynovitis, also in relation to synovitis, at small-joints associated with MS in patients presenting with undifferentiated arthritis (UA) and RA.

Methods

Patient population

We studied cross-sectional data of 286 consecutive patients from the Leiden Early Arthritis Clinic (EAC)-cohort included between June 2013-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) that underwent baseline gadolinium-enhanced MRI were selected (supplementary Figure 9.2). The clinical diagnosis was made by the treating rheumatologist. RA was further verified by

fulfilling the classification-criteria during the first-year. Patients with missing MRI-scans were excluded (n=65); they were not different from included patients (Table S1).

Baseline questionnaires, 66-swollen and 68-tender joint counts (66-SJC,68-TJC), 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.

Morning stiffness measurements

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

MRI scanning and scoring

Baseline 1.5T MRI were made (before any DMARD-initiation), of MCP(2-5)-, wrist- and MTP(1-5)-joints of the most affected side (or dominant side in case of equal symptoms). NSAIDs were stopped 24hrs before MRI. Scans were performed between 9am-16pm. and scored in line with the OMERACT-RAMRIS-method by two independent readers; mean scores of both readers were calculated. Semi-quantitative scores ranged from 0-3 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 ≥1 joint, which was present in <5% of age-matched healthy controls (described supplementary) .

Statistics

Associations between MS and MRI-detected synovitis and tenosynovitis were tested with logistic-regression (MS entered as dependent; clinical-, imaging-findings as independent variables). The explained variance was assessed by the Nagelkerke R^2. As synovitis/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 was examined,[13] by the relative risk excess (RERI), synergy index (SI) and attributive proportion (AP). In the absence of an interaction, RERI, AP equal 0 and SI equals 1,[13] and described supplementary.
Sensitivity analyses were performed, firstly in RA-patients (excluding UA-patients), secondly for MS-duration ≥30 minutes. Thirdly, as MS is often experienced at the hands, MRI-detected inflammation was assessed in hand-joints(excluding MTP-joints).
IBM SPSS v23 was used. P-values <0.05 were considered significant.

Results

Patient characteristics

Baseline characteristics are shown in Table 1. 40% experienced MS. They had higher 66-SJC and CRP (Table 9.1).

Associations between tenosynovitis and synovitis with morning stiffness

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 9.1).

Tenosynovitis was present in 70% and more often in patients with MS (80% versus 65%); OR 2.11 (1.21;3.68). Synovitis was present in 49% and more often in patients with MS (58% versus 44%; OR 1.79 (1.11;2.91)) (Table 9.2). The explained variance (R^2) ranged between 4-5% (Table 9.2).

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 imaged joints. Presence of simultaneous synovitis/tenosynovitis had the strongest association with MS (OR 2.43 (1.30;4.54)), while synovitis without tenosynovitis was not

Table 9.1: Baseline characteristics of RA and UA-patients studied and odds ratios with morning stiffness

	All patients (n=286)		MS present (n=113)		MS absent (n=173)		OR* (95%CI)
Age, 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)
66-Swollen joint count, median (IQR)	3	(1-8)	6	(1-6)	2	(1-6)	1.08 (1.03; 1.13)
Symptom duration in weeks, median (IQR)	10	(5-27)	9	(4-27)	11	(5-27)	1.00 (0.99; 1.01)
CRP increased (≥5mg/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)

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 on having MS than patients with a normal CRP, and for 66-SJC 1.08, meaning that per increase in swollen joint the patient had a 1.08 higher odds on MS. *OR, odds ratio with MS, morning stiffness. ACPA, anti-citrullinated peptide antibody (anti-CCP2, EliA CCP, Phadia, the Netherlands, positive if ≥7 U/mL); RF, immunoglobulin M-rheumatoid factor (RF) (positive if ≥3.5 IU/mL); CRP, c-reactive protein (positive if ≥5mg/L); SD, standard deviation; IQR, Inter quartile range.

associated in categorized analyses (OR 0.85 (0.21;3.47) (Table 9.2, Figure 9.1).
The presence of an additive interaction between synovitis and tenosynovitis was explored; although the 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 9.2, Figure 9.1)

Sensitivity analyses

Analyses in RA-patients (n=168, Table 9.3), showed similar results for tenosynovitis and synovitis with MS (OR 1.82 (0.75;4.42), (Table 9.4)).
Analyses of MS ≥30 minutes, were also similar. Simultaneous presence of tenosynovitis/synovitis associated with MS (OR 2.65 (1.45;4.84), (Table 9.5)).

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 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 have a greater contribution to the symptomatology of MS.
Most previous studies that investigated associations between inflammation and MS focussed 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 swollen joint counts was

Table 9.2: Baseline characteristics of RA and UA-patients studied and odds ratios with morning stiffness

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)	

Associations of morning stiffness with presence of MRI-detected tenosynovitis and synovitis and categorized analyses.
*OR (95% CI): Odds ratios with 95% confidence intervals.

reported,[1] which was 1.08 here. To the best of our knowledge, this was the first study that examined the effect of MRI-detected tenosynovitis in relation to MS, also taking simultaneous presence of synovitis into account. The association between MRI-detected inflammation and MS were similar in RA or the total group.

Previous studies have shown that a duration >60 minutes was specific for RA but >30 minutes 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

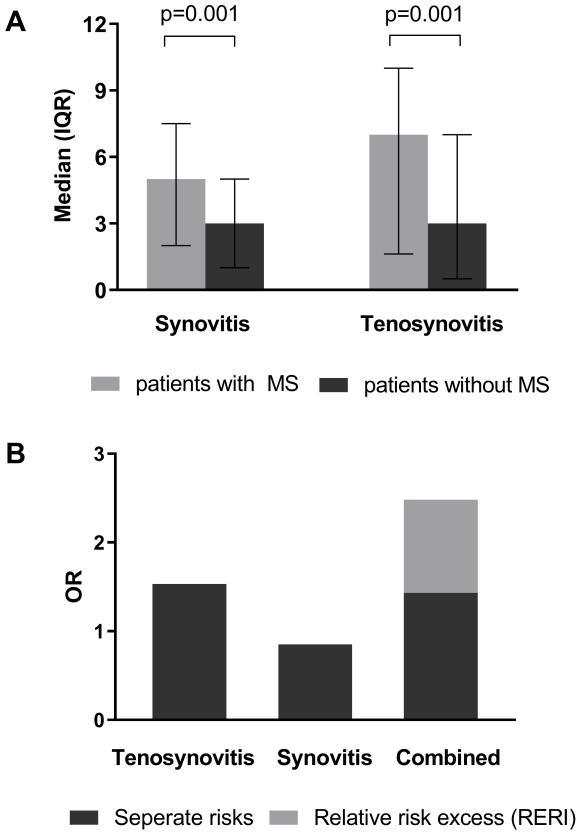

Figure 9.1: Associations of morning stiffness with (A) MRI-detected tenosynovitis and synovitis-scores and (B) evaluation of the presence of an additive interaction.
Legend. A shows median (interquartile range, IQR) synovitis and tenosynovitis-scores in patients with and without MS. B illustrates the additive effect of the combined presence of synovitis and tenosynovitis. RERI was 1.05 (–0.52;2.62), AP 0.43 (–0.18;1.05), SI 3.78 (0.05;270.0).

not exist. We collected data of MS-duration but not of MS-severity. Previous reviews concluded that there is insufficient evidence to prioritise a measure for MS.[4, 14] Whether the association of MRI-detected inflammation with MS-severity is stronger than that of MS-presence is subject for further studies.

Second, MRI-scans were performed anytime 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.

It is surprising that the biologic 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/surrounding synovial compartment follow the circadian rhythm. As synovitis/tenosynovitis often occur simultaneously, we hypothesized that this co-occurrence might engrave MS. Indeed we observed the highest association for the 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.

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

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Supplementary data

Supplementary data are online available.

Supplementary figure

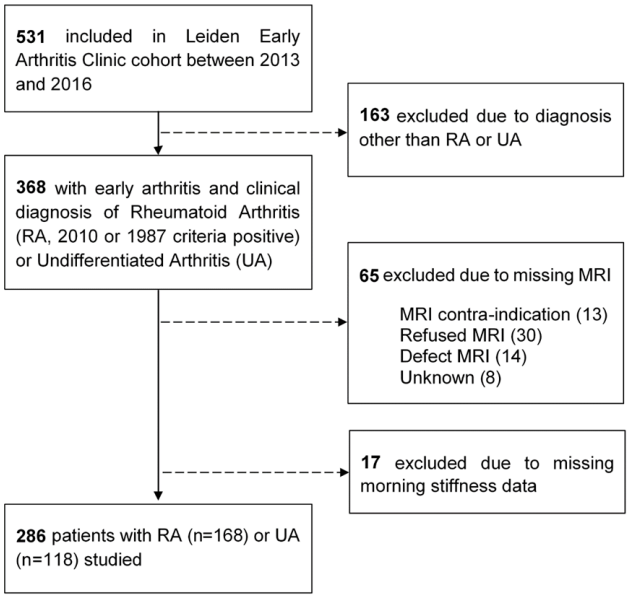

Figure 9.2: Flowchart of patient selection

Supplementary tables

Table 9.3: Sensitivity analyses: baseline characteristics of patients with RA (fulfilling 2010- and/or 1987-classification criteria) and odds ratios for presence of morning stiffness

	All patients (n=168)		MS present (n=86)		MS absent (n=82)		OR* (95%CI)
Age, mean (SD)	59	(14)	61	(13)	57	(16)	0.99 (0.96; 1.01)
Female, n (%)	111	(67)	60	(70)	51	(62)	1.40 (0.74; 2.66)
66-Swollen joint count, median (IQR)	6	(3-11)	5	(2-9)	8	(4-12)	1.04 (0.99; 1.09)
Symptom duration in weeks, median (IQR)	13	(6-29)	16	(7-33)	11	(6-29)	0.99 (0.98; 1.00)
CRP increased (≥5mg/L), n (%)	110	(67)	52	(61)	58	(72)	1.60 (0.84; 3.07)
RF positive (≥3.5 IU/mL), n (%)	94	(57)	49	(58)	45	(55)	1.02 (0.58; 1.79)
ACPA positive (≥7 U/mL), n (%)	74	(45)	42	(49)	32	(40)	0.67 (0.36; 1.24)

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 on having MS than patients with a normal CRP, and for 66-SJC 1.08, meaning that per increase in swollen joint the patient had a 1.08 higher odds on MS. *OR, odds ratio with MS, morning stiffness. ACPA, anti-citrullinated peptide antibody (anti-CCP2, EliA CCP, Phadia, the Netherlands, positive if ≥7 U/mL); RF, immunoglobulin M-rheumatoid factor (RF) (positive if ≥3.5 IU/mL); CRP, c-reactive protein (positive if ≥5mg/L); SD, standard deviation; IQR, Inter quartile range.

Table 9.4: Sensitivity analyses in patients with RA (fulfilling 2010- and/or 1987-classification criteria) for odds ratios for presence of morning stiffness (>60 minutes) and categorized analyses.

Presence of feature		OR (95% CI)	R^2
	Synovitis	1.38 (0.74; 2.58)	0.01
	Tenosynovitis	1.77 (0.80; 3.91)	0.02
Categorized features			
Synovitis	Tenosynovitis	OR (95% CI)	
-	-	1.0 (ref)	0.02
+	-	0.80 (0.12; 5.20)	
-	+	1.45 (0.54; 3.95)	
+	+	1.82 (0.75; 4.42)	

*OR (95% CI): Odds ratios with 95% confidence intervals.

Table 9.5: Sensitivity analyses for when MS was defined as a duration >30 minutes; odds ratios and categorized analyses

Presence of feature		OR (95% CI)	R^2
	Synovitis	1.96 (1.21; 3.18)	0.04
	Tenosynovitis	2.17 (1.29; 3.66)	0.04
Categorized features			
Synovitis	Tenosynovitis	OR (95% CI)	
-	-	1.0 (ref)	0.06
+	-	0.77 (0.23; 2.68)	
-	+	1.44 (0.75; 2.78)	
+	+	2.65 (1.45; 4.84)	

*OR (95% CI): Odds ratios with 95% confidence intervals.