Diagnostic values of history and clinical examination to predict ultrasound signs of chronic and acute enthesitis

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Abstract

Objective

To examine the diagnostic values of history of chronic enthesitic pain and clinical signs of acutely inflamed entheses to predict ultrasound (US) signs of enthesitis.

Methods

Cohort study of 21 consecutive rheumatic out-patients (female/male 18/3) with suspected multiple enthesitis and 12 controls (female/male 10/2). 429 enthesal sites according to the Maastricht Ankylosing Spondylitis Entheses Score (MASES) were evaluated by history, clinical examination, B-mode and power Doppler US. Sensitivity and specificity of history suggesting chronic enthesitic pain and clinical examination suggesting acute enthesitis were calculated using corresponding US findings as reference standard.

Results

Diagnostic accuracy widely varied between different MASES sites. Sensitivity and specificity of selected MASES points were 66.7 – 86.4 % and 85.0 – 91.7 % for history and 71.4 – 87.0 % and 47.4 – 75.0 % for clinical examination, respectively ($p<0.05$ for each).

Conclusion

At specific enthesal sites, history of chronic enthesitic pain and clinical signs of acute inflammation are sensitive and specific for the diagnosis of chronic and/or acute inflammation.

Key words

Sensitivity and specificity, spondylarthritis, enthesopathy, musculoskeletal diseases, medical history taking, ultrasonography.

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Introduction

Inflammation at enthesal sites frequently occurs in rheumatic disorders, and current classification criteria for spondyloarthritis (SpA) include the presence of enthesitis (1). Enthesitis has been considered to be the initial site of inflammation in SpA, which only later extends to juxtaposed synovial tissues (2). Enthesitic pain is associated with a higher SpA disease activity and can lead to restriction of daily activities (3). Entheses are defined as areas where tendons, ligaments or joint capsules attach to bone. They are metabolically highly active and extremely sensitive because of their high content of nerve terminals (4).

Diagnosis of enthesitis is difficult, and only a few studies have determined the diagnostic value of clinical assessments in enthesal sites (5-10). These studies showed a low sensitivity and specificity for clinical examination, but most of them did not compare the enthesitic sites according to structured instruments such as the Mander enthesitis index (MEI, 66 entheses) (11) or the Maastricht Ankylosing Spondylitis Entheses Score (MASES, 13 entheses) (12). Interestingly, all but one of these studies restricted the evaluation of entheses to the lower limbs, and enthesitis was assessed using MASES only in a small cohort of patients suffering from ankylosing spondylitis with divergent results considering clinical and ultrasound examination of entheses (10). Current imaging techniques to detect enthesopathies include plain radiography, B-mode Ultrasound (US), power Doppler US and magnetic resonance imaging (MRI) (6-8, 13, 14). So far the few studies comparing US and MRI suggest that US may perform even better than MRI with a greater sensitivity, lower costs, and less time consumption (13, 14). US can thus be considered as the most reliable imaging technique to diagnose enthesitic inflammation at multiple sites.

In this study we prospectively assessed the diagnostic accuracy of history for chronic enthesitic pain and clinical examination to detect chronic and acute enthesitis verified by sonography, respectively.

Methods

History and clinical examination

This study was conducted in a rheumatological and radiological out-patient clinic (tertiary care unit). Twenty-one patients (median age 51 years, range 30-75; female/male ratio 18/3) with suspected chronic and/or acute enthesitis at more than two MASES points were consecutively enrolled. A control group consisted of 8 patients with rheumatoid arthritis (median age 65 years, range 56-77; female/male ratio 7/1) and 4 patients with non-rheumatic diseases (median age 55 years, range 45-65; female/male ratio 3/1; hypertension, n=2; anemia, n=1 and multiple myeloma, n=1). The MASES score includes entheses at the 1st and 7th costosternal joints, the posterior superior iliac spines (PSIS), the anterior superior iliac spines (ASIS), the iliac crests, the insertion of the Achilles tendons and the 5th lumbar spinous process. Each MASES enthesis was recorded by an experienced rheumatologist (MS) both for history of chronic inflammatory pain suggesting chronic enthesitis and clinical findings of tenderness indicating acute enthesitis (5). Chronic inflammatory pain was considered if at least three of the following criteria were present: pain lasting for more than three months, pain during night or in the early morning, improvement of pain by oral non-steroidal anti-inflammatory drug therapy (15), morning stiffness ≥30 minutes. Tenderness was elicited by pressure, mobilization, and contraction against resistance of the corresponding tendons. Oral and written informed consent was obtained from all participants according to the local ethics committee.

Five out of the 21 patients were diagnosed with ankylosing spondylitis, five with psoriatic arthritis, seven patients with undifferentiated SpA, one patient each with reactive arthritis and colitis-associated spondyloarthritis (1, 16). Six patients were HLA-B27 positive. Two patients (one HLA-B27 positive) with chronic low back pain and peripheral enthesitis did not fulfil the European Spondyloarthropathy Study Group (ESSG) preliminary criteria (1). Median Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

score was 65 mm (range 16-100) and median Bath Ankylosing Spondylitis Functional Index (BASFI) score was 45 mm (range 4-99). Median levels of erythrocyte sedimentation rate (ESR, according to Westergren method) were 16 mm/1st hour (range 2-50) and median levels of C-reactive protein (CRP, measured by nephelometric method) were 7 mg/l (range 1.5-38.3). The median actual disease activities estimated on a visual analogue scale (VAS, 0-100mm) by patients and the physician were 62 mm (range 0-100) and 53 mm (range 0-70), respectively.

Ultrasound performance and evaluation

US examination was performed subsequently after the rheumatological visit by an experienced radiologist (AK) blinded to the results of history and clinical examination. The patients were positioned on the examination table in a darkened room in which the temperature was held constant at 20°C. Examinations of the 1st and 7th costosternal joints, ASIS, and iliac crest were performed with the patients in supine position. The insertion of the Achilles tendons, the PSIS and the 5th lumbar spinous process were examined with the patients in prone position (10). Each examination took 20-30 minutes. Scan images were registered on the hard disc of the US unit and transferred to the local picture archiving and communication system (PACS). Following anatomical landmarks were used at the examined MASES entheses for longitudinal and transverse US scans: synchondrotic junction between sternum and 1st rib, insertion of subclavian muscle, insertion of costoclavicular ligament and sternal membrane (1st costosternal joints). Synchondrotic junction between sternum and 7th rib and origin of rectus abdominis muscle (7th costosternal joints). Insertion of the thoracolumbal fascia on the iliac tuberosity and insertion of the major gluteal muscle (PSIS). Insertion of the sartorius muscle and the tensor fascie latae muscle and the inguinal ligament (ASIS). Insertion of the gluteal aponeurosis, insertion of major/medium gluteal muscle, insertion of the iliacal part of latissimus dorsi muscle, insertion of oblique external abdominis muscle and insertion of iliocostalis lumborum muscle (iliac crests). Insertion of interspinale lumborum muscle and supraspinal ligament and thoracolumbal fascia (5th lumbar spinous process).

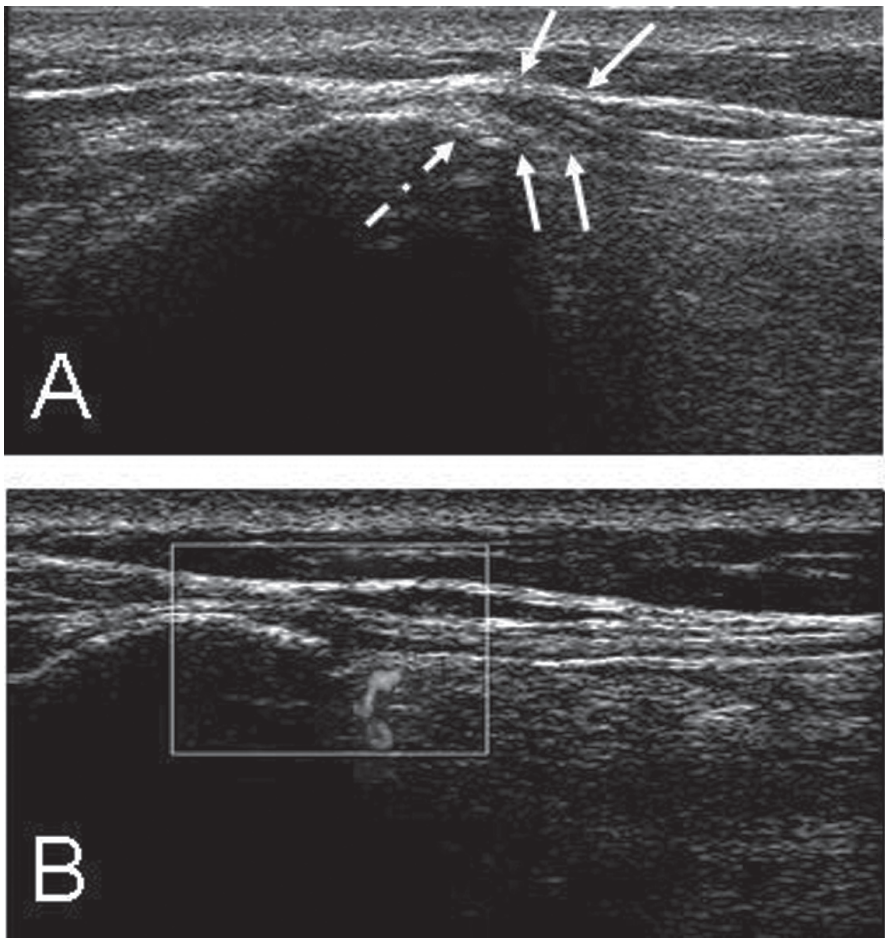

Fig. 1. B-mode ultrasound of the left posterior superior iliac spine (PSIS).
(**A**) Transversal gray scale ultrasound (US) of the left PSIS shows hypoechoic thickening of the enthesis (→) and cortical irregularity at enthesis site (⇢). (**B**) Power Doppler US shows no vascularity at the enthesis, only deeper and more superficially located vessels can be detected, consistent with inactive chronic enthesitis.

The US machine used was an Esaote unit (Technos MPX; Genoa, Italy) equipped with a LA424 14-8 linear array transducer. A frequency between 10-13 MHz was used for B- mode US depending on the depth of examined landmarks, *e.g.*, costosternal joints with 13 MHz, PSIS with 10 MHz. Power Doppler settings where standardized accordingly: a frequency 8.3 MHz and pulse rate frequency 500 cm/sec, with low wall filter and medium persistence remained fixed throughout the study. These settings were chosen to maximize sensitivity to low-velocity and low-volume blood flow. The Power Doppler gain was optimized by increasing gain until noise appeared and then reducing gain just enough to suppress the noise. The window of the color box was restricted to the areas studied: After visualization of color-flow signals, pulse-waved spectral Doppler imaging was performed using the lowest filter setting and the smallest scale available that would display the Doppler waveforms as large as possible without aliasing. A spectral Doppler tracing was obtained to confirm that the Power Doppler signals represented true arterial or venous flow.

In B-mode, extraarticular cortical irregularities including erosions (defined as cortical breakage with a step down contour defect within the areas where tendons, ligaments or joint capsules attach to bone) with or without new bone

Table I. Distribution of enthesitis according to the "Maastricht Ankylosing Spondylitis Entheses Score" (MASES). Percentages of patients positive for history of chronic enthesitic pain, clinical signs of acute enthesitis, ultrasound (US) detected chronic and acute lesions at each MASES site.

	Patients (%) positive for history of chronic enthesitic pain		Patients (%) positive for clinical signs of acute enthesitis		Patients (%) positive for US detected chronic lesions		Patients (%) positive for US detected acute lesions	
	Right	Left	Right	Left	Right	Left	Right	Left
1st costosternal joints	31.0	35.7	31.0	40.5	40.5	38.1	28.6	26.2
7th costosternal joints	23.8	23.8	19.0	21.4	28.6	31.0	19.0	14.3
Anterior superior iliac spines	16.7	16.7	11.9	11.9	19.0	23.8	7.1	4.8
Iliac crests	26.2	26.2	19.0	26.2	26.2	26.2	16.7	14.3
Posterior superior iliac spines	31.0	33.3	31.0	33.3	33.3	33.3	16.7	14.3
5th Lumbar spinous process	81.0		76.2		47.6		14.3	
Insertions of Achilles tendons	38.1	35.7	21.4	16.7	33.3	33.3	7.1	9.5

Table II. Diagnostic value of history and clinical examination to detect ultrasound verified enthesitis.
Diagnostic values for history of chronic enthesitic pain to detect ultrasound (US) signs of chronic enthesitic lesions and clinical signs of acute enthesitis to detect US signs of acute lesions. LR+, positive likelihood ratio; LR-, negative likelihood ratio. Bonferroni adjusted *p*-values are shown with $p<0.01$ as highly significant, $p<0.05$ considered as significant and $p<0.2$ as a trend, ns, not significant.

	Sensitivity, %	Specificity, %	LR+	LR-	*p*-value
History *vs*. US verified chronic lesions (all sites)	72.1	63.0	1.9	0.4	<0.001
1st costosternal joints					ns
7th costosternal joints	72.0	88.2	6.1	0.3	<0.001
Iliac crests	86.4	85.0	5.8	0.2	<0.001
Anterior superior iliac spines	66.7	91.7	8.0	0.4	<0.001
Posterior superior iliac spines					ns
5th lumbar spinous process					ns
Insertions of Achilles tendons					ns
Clinical examination vs. US verified acute lesions	67.5	58.2	1.6	0.6	<0.001
1st costosternal joints	87.0	47.4	1.7	0.3	0.048
7th costosternal joints	71.4	75.0	2.9	0.4	0.012
Iliac crests	69.2	65.6	2.0	0.5	0.108
Anterior superior iliac spines					ns
Posterior superior iliac spines					ns
5th lumbar spinous process					ns
Insertions of Achilles tendons					ns

formation (step up bony prominence at the end of the normal bone contour), and local hypoechoic swelling of the entheses (indicated by a convex surface of the enthesis adjacent to bone) without signs of vascularization were defined as sonographic signs of chronic enthesitis (Fig. 1) (5, 17). To detect acute enthesitis, blood flow was examined at the enthesis using power Doppler mode. Since vascularization was never found in normal peripheral entheses according to D'Agostino *et al*. (5) and our own experience (unpublished observations), detection of vascularization was defined as a sign of acute enthesitis (Fig. 1). To exclude a different pain threshold as a possible confounding factor between patients and healthy individuals MASES points without US signs of chronic or acute enthesitic lesions were used as controls (18).

Statistical analysis

US examinations were considered as the reference standard, and sensitivities, specificities, positive (sensitivity/1-specificity), and negative (1-sensitivity/specificity) likelihood ratios were calculated using the Chi-square and Fishers' exact test with Bonferroni correction for multiple testing. The Spearman's Rho test was used to examine for possible correlations. All statistics were performed using the SPSS program, version 11.0 (Chicago, IL, USA) and the Java supported biometry of the University of Münster.

Results

The presence of three or more sites of enthesitis was verified by US in all 21 patients with suspected multiple enthesitis. In these patients enthesitis had not been diagnosed before, although pain as a major symptom of enthesitis had already been reported for an average of 8.4 (median 5, range 0.5-35) years. In the control group no patient had multiple enthesitis as determined by US.

In patients with definite multiple enthesitis, out of the 273 enthesal sites (13 sites x 21 patients) assessed, 159 sites (median 7/patient, range 0-13) were recorded as chronic painful and 135 (median 7/patient, range 1-11) showed signs of acute inflammation at clinical examination. US signs of chronic and acute lesions were present in 164 (median 7/patient, range 3-12) and 78 (median 4/patient, range 0-12) enthesal sites (Table I). Diagnostic values of history and clinical examination are summarized in Table II.

Fourteen patients (66.7%) had elevated levels of ESR and/or CRP. No significant association of ESR, CRP levels, HLA-B27, morning stiffness, disease duration, and patients' age with the number of entheses suspicious for enthesitis and the prevalence of US signs of chronic or acute lesions was found after adjustment for multiple testing (data not shown).

In the control group, out of the 156 enthesal sites (13 sites x 12 patients) assessed, only 1 site was recorded as chronic painful and 6 sites (2 patients with 1 and 2 patients with 2 sites each) showed signs of acute inflammation at clinical examination. US signs of chronic and acute lesions were present in 4 (2 patients with 2 sites each) and 2 (2 patients) enthesal sites, respectively.

Discussion

This systematic study with a validated set of entheses (MASES) shows that history of chronic enthesitic pain and clinical signs of acute enthesitis have a good diagnostic value to predict corresponding US signs of enthesitis at least at certain MASES points (Table II). The significant sensitivity of 72.1% and specificity of 63.0% of history taking to detect chronic enthesitis at any MASES enthesis, and according values of 67.5% and 58.2% of clinical signs to detect acute enthesitis are superior to all previous data reported for other enthesitic sites (5-10). This finding can at least partially be explained by our distinction between chronic and acute signs of enthesitis not only by sonographic criteria (as described by Alcalde M. *et al*.) (9), but also by clinical criteria. Indeed, many chronically inflamed entheses do not show signs of active inflammation and, vice versa, inflammation may have started only recently before occurrence of ultrasound signs of chronic lesions.

Clinical signs of chronic enthesitis such as non-tender swelling and/or induration of entheses may principally also indicate chronic enthesitis. However, such chronic signs of enthesitis were not observed in our cohort and were thus not compared with corresponding US findings. The sonographic correlate of history of acute enthesitis, reported as a past but not present tenderness of entheses, was also not evaluated in the present study due to its cross-sectional design.

Taking history of chronic pain and clinical examination of entheses are basic skills of each physician. The positive likelihood ratios of history and clinical examination then emphasize the need for subsequent imaging techniques like US to ascertain the presence of enthesitis, although US of the enthesis depends on the operator's experience and the examination is time-consuming. Therefore we propose that in clinical practice US examination should focus only on those enthesal sites with the highest likelihood of changes according to history and clinical examination. The observation that one third of our patients had no laboratory alteration further stresses the importance of history and clinical examination to suspect enthesitis. Notably, 8.4 years passed until first detection of multiple sites of enthesitis in our patients. Others had already pointed out that enthesitis coincides or possibly precedes sacroileitis (2), and earlier recognition of enthesitis may reduce time until diagnosis of SpA (19).

It is improbable that the diagnostic accuracy of history and clinical examination at the so far insignificant MASES points would be clinically meaningful in a larger study cohort. For these MASES points, power calculation showed that up to 625 patients would be required to achieve significance given an 80% power of the study and using Bonferroni adjustment for multiple testing. As reasons for the varying performances of history and clinical examination we can only speculate that chronic pain and tenderness are differently realized at certain MASES sites. For example, in the lumbosacral area the distinction between entheses and other structures like muscles or the sacroiliac joints is more difficult. Similarly the insertions of the Achilles tendons are surrounded by many structures such as muscles and the retrocalcaneal bursa which may imitate enthesitic pain.

There are some important caveats to our study. One limitation is that in clinical practice there is currently no "reference standard" for the diagnosis of enthesitis. The histological assessment of entheses is certainly more specific, but obsolete to be performed at multiple sites. Alternatively, we used US as an accepted imaging tool to diagnose chronic and acute enthesitis at multiple sites. US has been performed by a single investigator blinded to the rheumatologists' clinical findings. We concede that neither repeated clinical and US assessments were performed in order to calculate inter- and intra-observer reliabilities nor intra-operator reliability was assessed to determine the consistency of longitudinal and transverse scan-results by the same operator. However, a good inter-observer reliability of sonography of entheses in SpA patients was reported earlier (9). Other limitations of this study are the low number of patients and controls as well as the fact that MASES has not been developed for patients with suspected multiple enthesitis. Indeed, MASES was created to assess enthesitis in ankylosing spondylitis and was based on the statistically (but not anatomically) most relevant sites of MEI (12). The MEI score would have provided a more complete assessment of enthesitis. However, in clinical practice MEI is not feasible because of the 66 enthesal sites, which prompted us to prefer the MASES despite the shortcomings mentioned.

To avoid different pain perception as a possible confounding factor we decided to exclude the control group from sensitivity and specificity calculations, as previous reports had shown different pain perception between patients with ankylosing spondylitis, rheumatoid arthritis, and healthy controls (18). MASES points without US signs of enthesitis of the same patients were used as "internal" controls. With this study design we certainly increased the pretest likelihood to detect enthesitic sites, but excluded any bias due to varying pain thresholds. Besides, our data confirm earlier observations that chronic and acute enthesitis are rare in control patients without clinical suspicion of enthesitic sites (9). Sensitivity and specificity calculations of history and clinical signs of enthesitis to predict sonographically confirmed enthesitis were thus inappropriate in the control group.

In conclusion, positive history as well as clinical examination have a good diagnostic value in the diagnosis of enthesitis at predefined MASES points and may help physicians to early diagnose SpA.

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