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ORIGINAL ARTICLE

Inflammatory pain pattern and pain with lumbar extension associated with Modic 1 changes on MRI: a prospective case–control study of 120 patients

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Abstract
Purpose To compare, in a case–control study, clinical characteristics of patients with low back pain (LBP) with and without Modic 1 signal changes on MRI.
Methods Patients with chronic non-specific LBP and a recent (<6 months) MRI were prospectively screened and included in Modic 1 group or control group. Patients in control group were age- and gender-matched with patients with Modic 1 group. Pain characteristics, including night pain and worse pain on waking and morning stiffness, were recorded. The presence of at least one of these three characteristics indicated an inflammatory pain pattern. Patients were evaluated by questionnaires and physical examination (including lumbar range of motion). Data were analyzed by univariate and multivariate analyses.
Results 120 patients were included (60 in each group). The groups did not differ in sedentary work ($p = 0.25$), morning stiffness for >60 min ($p = 0.19$), waking at night ($p = 0.08$), worse pain on waking ($p = 0.09$), back stiffness ($p = 0.12$), or pain with flexion ($p = 0.87$). Modic 1 patients more frequently exhibited an inflammatory pain pattern ($p = 0.006$), worse pain with lumbar extension ($p < 0.005$) and responded better to oral steroids ($p = 0.004$) than did controls. On multivariate analysis, Modic 1 changes were associated with sedentary work [odds ratio 0.22 (95 % confidence interval 0.05–0.93)], pain with lumbar extension [11.2 (3.1–40.4)] and an inflammatory pain pattern [4.5 (1.2–16.9)].
Conclusions Characteristics of patients with LBP and Modic 1 changes on MRI consist of an inflammatory pain pattern and pain with lumbar extension.
Level of evidence 3b.

Keywords Modic changes · Low back pain · Physical examination · Diagnosis · Magnetic resonance imaging

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Introduction

Modic changes represent the signal intensity changes of vertebral end plates and subchondral bone on MRI. Modic changes were first described by de Roos et al. [1] and classified by Modic et al. [2, 3] into three groups. Modic 1 changes correspond to vertebral body oedema [2] [hypointense signal in T1-weighted imaging (T1WI) and hyperintense signal in T2-weighted imaging (T2WI)]. Modic 2 changes refer to fat lesions (hyperintense signal in T1WI and hyperintense signal in T2WI), and Modic 3 changes indicate subchondral bone sclerosis (hypointense signal in T1WI and hypointense signal in T2WI). Modic 1 changes are rare in an asymptomatic population and are

frequently associated with low back pain (LBP) [4]. Subgrouping patients may be important because symptoms and treatment may differ according to Modic changes.

The clinical characteristics associated with Modic 1 changes should be defined to give arguments for the clinician to perform MRI to confirm the diagnosis. The presence of Modic 1 changes seems to be associated with inflammatory clinical, biological and radiological characteristics. A study by Kjaer et al. [5] attempted to define the clinical features associated with Modic changes: increased intensity of reported LBP and increased intensity of pain with lumbar movement. However, the clinical features of patients with Modic 1 changes were not studied separately from patients with Modic 2 or 3 changes or from those with disc degeneration; furthermore, the characteristics of the pain pattern were not analyzed.

Hypersignals on MRI could be explained by a local inflammation phenomenon at the vertebral end plate level [6]. Biopsies of the Modic 1 vertebral body show replacement of marrow by richly vascularized fibrous tissue [2] and elevated number of tumor necrosis factor-immunoreactive cells in the intervertebral disc [7]. In addition, increased levels of high-sensitivity C-reactive protein were reported in patients with chronic LBP and Modic 1 changes by Rannou et al. [8]. In this study, patients with Modic 1 changes seem to have a longer duration of morning stiffness and worst painful moment at night and morning.

Causes of Modic changes were not clear-cut [6] and degenerative, immunologic or infectious causes were suggested. This last hypothesis was recently highlighted by a possible efficacy of antibiotics for patients with Modic 1 changes [9]. However, whether specific clinical features are associated with MRI changes in vertebral body marrow is still unclear.

This study aimed to compare the clinical characteristics of LBP in patients with and without Modic 1 changes.

Methods

Study patients

From December 2008 to December 2010, patients referred for chronic LBP to outpatient clinics of rheumatology departments of two centers in France and one center in Switzerland were prospectively screened. Patients were included, after obtaining informed consent, if they had chronic LBP and had undergone MRI testing in the preceding 6 months. If sciatica was present, it had to be less painful than back pain. Exclusion criteria were specific spinal pathology, and care was taken to exclude patients with spondyloarthritis.

Data collection

Data were collected using questionnaires. In the first part, patients completed a questionnaire about demographics (gender, age, sedentary work, sick leaves and their durations), and pain characteristics (duration since the first LBP episode, duration since pain heightening, presence of a triggering factor, associated sciatica, morning stiffness, waking at night because of LBP, maximal diurnal intensity pain period) as well as a standardized disability questionnaire validated in French [Dallas Pain Questionnaire (DPQ)] [10]. Inflammatory criteria were defined after review from recent literature on inflammatory back pain [11, 12], and from inflammatory criteria of ankylosing spondylitis [13–17]. An inflammatory pain pattern was defined by the presence of at least one of three characteristics: maximal pain on morning, waking at night because of pain, and morning stiffness for longer than 60 min. In the second part, the rheumatologist completed a questionnaire about the physical examination (presence and location of back stiffness, scoliotic list, side of back pain, presence of lumbar pain with flexion or extension), MRI findings (assessed by a radiologist and a rheumatologist according to presence or absence of Modic 1 changes, localization, and side of Modic 1 changes if available) and treatment [use and efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, epidural corticosteroid injection and/or lumbar brace].

Patients were separately included in the two groups according to the MRI results and were matched for age and gender. Informed consent was obtained from all patients for inclusion in the study.

Statistical methods

We hypothesized a difference of 28 % of the frequency of inflammatory pain pattern between the groups, with a frequency of 50 % in the non Modic group, alpha risk = 5 % and power of 90 %. Thus, we needed 60 patients per group to demonstrate a clinical difference between groups. Quantitative and categorical data were analyzed by univariate analysis with Wilcoxon and Fisher tests, respectively. The association of demographic and clinical characteristics and MRI findings was examined by multivariate analysis (logistic regression, stepwise, backfit), not including data on prescribed treatment and the clinical response. SAS v9.1 (SAS Inst., Cary, NC) was used for data analysis. $p < 0.05$ was considered statistically significant.

Results

We prospectively included 120 patients with LBP (60 patients in each group): patients with Modic 1 changes and

Table 1 Demographic and clinical characteristics of patients with low back pain with and without (control) Modic 1 changes on MRI

Characteristics	Modic 1 patients $N = 60$	Control patients $N = 60$	p
Demographic characteristics			
Female patients, *n* (%)	43/60 (72)	43/60 (72)	
Age, years (SD)	45 (±11)	45 (±11)	
Physical work, *n* (%)	24/56 (43)	19/59 (32)	0.25
Sick leaves, *n* (%)	11/60 (18)	10/60 (17)	0.81
Duration of sick leaves week, median (IQR)	22 (3–128)	8 (4–10)	0.49
Clinical characteristics			
No. of years since the first episode, median (IQR)	6 (4–18)	4 (2–14)	**0.03**
No. of months since the flare-up pain, median (IQR)	12 (7–33)	12 (8–21)	0.40
Presence of a triggering factor, *n* (%)	33/59 (56)	27/59 (46)	0.36
Sciatica, *n* (%)	33/58(57)	36/56 (64)	0.42
Morning stiffness for >60 min, *n* (%)	16/59 (27)	8/59 (14)	0.19
Waking at night because of LBP, *n* (%)	25/59 (42)	15/57 (26)	0.08
Maximal pain intensity on waking up, *n* (%)	28/60 (47)	19/60 (32)	0.09
Inflammatory pain pattern, *n* (%)	48/60 (80)	33/60 (55)	**0.006**
DPQ impact on			
Daily activities, mean (SD)	62 (±18)	55 (±19)	0.053
Work/leisure, mean (SD)	53 (±28)	53 (±26)	0.88
Anxiety/depression, mean (SD)	35 (±28)	38 (±27)	0.56
Social activities, mean (SD)	29 (±27)	31 (±23)	0.38
Physical examination			
Back stiffness, *n* (%)	36/56 (64)	26/53 (49)	0.12
Scoliotic list, *n* (%)	8/56 (14)	8/56 (14)	1.00
Pain with lumbar flexion, *n* (%)	32/58 (55)	29/59 (54)	0.87
Pain with lumbar extension, *n* (%)	47/59 (80)	25/54 (46)	**<0.005**
Lumbar pain on straight-leg-raising test, *n* (%)	16/59 (27)	15/53 (28)	0.88
Medications			
NSAID prescription, *n* (%)	44/50 (88)	51/58 (88)	1.00
Good clinical response to NSAID, *n* (%)	18/51 (35)	14/43 (33)	0.83
Oral corticosteroid prescription, *n* (%)	34/58 (59)	15/50 (30)	**0.0037**
Good clinical response to oral corticosteroids, *n* (%)	17/34 (50)	1/15 (7)	**0.0039**

Bold values indicate $p < 0.05$

IQR interquartile range, *DPQ* Dallas Pain Questionnaire (maximum score was 100, high score mean high impact), *LBP* low back pain, *NSAID* non-steroidal anti-inflammatory drug

age–gender matched control patients. The mean age of patients was 45 ± 11 years; 72 % of patients were female. On univariate analysis, the groups did not differ in heavy physical work or sick leaves and their durations (Table 1). Duration of LBP was longer for Modic 1 than for control patients (6 vs. 4 years, $p = 0.03$). By contrast, the groups did not differ in time elapsed since the last flare of pain, presence of a triggering factor, leg pain, morning stiffness for longer than 60 min, waking at night, or maximal pain on waking up. The inflammatory pain pattern (at least one of morning stiffness for longer than 60 min, waking at night, maximal pain when waking up) was significantly more frequent in Modic 1 than control patients (80 vs. 55 %, $p = 0.006$).

The groups did not differ in responses to any part of the DPQ (i.e. daily activities, work/leisure, anxiety/depression, social activities). The presence of pain with extension was more frequent in Modic 1 than control patients (80 vs. 46 %, $p < 0.005$). However, the groups did not differ in back stiffness, scoliotic list, pain with lumbar flexion, or lumbar pain on straight-leg-raising test. Data for the clinical side of back pain and side of Modic 1 changes on MRI were available for 51 patients (Table 2). The side of back pain was significantly associated with the side of Modic 1 changes on MRI ($p < 0.001$). Pain with extension was not associated with posterior localization of Modic 1 changes ($p = 0.68$).

Oral corticosteroids were prescribed more frequently (59 vs. 30 %, $p = 0.037$) and were more effective (50 vs. 7 %, $p = 0.039$) for Modic 1 than control patients. The groups did not differ in number of prescriptions or effectiveness of NSAIDs. Multivariate analysis revealed an association of the following clinical features and Modic 1 changes: pain with lumbar extension [odds ratio (OR) 11.2 (95 % confidence interval 3.1–40.4)], inflammatory pain pattern [4.5 (1.2–16.9)] and physical work [4.54 (1.08–20)] (Table 3). Sensitivity of the former two factors was high,

Table 2 Relationship between clinical side of back pain and lateralization of Modic 1 changes on MRI

	No Modic 1 lateralization, *n*	Right Modic 1 lateralization, *n*	Left Modic 1 lateralization, *n*
Right back pain lateralization, *n*	2	13	1
No back pain lateralization, *n*	12	7	2
Left back pain lateralization, *n*	4	2	8

Table 3 Multivariate analysis on demographic and clinical characteristics associated with Modic 1 group

	OR	95 % CI
Physical work	4.54	1.08–20
Pain with lumbar extension	11.2	3.1–40.4
Inflammatory pain pattern	4.5	1.2–16.9

OR odds ratio, *95 % CI* 95 % confidence interval

Table 4 Sensitivity and specificity of significant findings on multivariate analysis associated with Modic 1 group

	Sensitivity (%)	Specificity (%)
Physical work	43	68
Pain with lumbar extension	79	53
Inflammatory pain pattern	80	45

79 and 80 %, respectively, and specificity moderate, 53 and 45 %, respectively (Table 4).

Discussion

The major finding of our prospective case–control study was that patients with LBP and Modic 1 changes on MRI exhibited more frequently an inflammatory pain pattern and pain during back extension than did other patients with LBP. Other findings were that physical jobs were a risk factor for Modic 1 changes and that the side of LBP did correspond to the side of the Modic 1 changes on MRI.

This study strengthens the fact that inflammatory back pain increases the probability of Modic 1 changes. None of the single variables sufficiently differentiated Modic 1 changes from mechanical LBP, but the presence of inflammatory pain pattern (i.e. presence of at least one of these three features: maximal pain on morning, waking at night because of pain, or morning stiffness for longer than 60 min) has enough sensitivity to be used as a screening tool to detect Modic 1 changes, as was shown in ankylosing spondylitis [18]. These results are in agreement with the study by Maigne and Balard, [19], who reported a positive response to a short course of oral steroids in patients with LBP and the presence of pain at night, worse pain on waking up and pain with lumbar extension. Our results also agree with Rannou et al. [8], who in a pilot study reported an association of the worst painful moment during late night and morning and Modic 1 changes and a possible association of longer duration of morning stiffness. Presence of inflammatory characteristics of pain must be linked with radiological and biological findings suggesting an inflammatory mechanism [6]. Increased blood levels of high-sensitivity C-reactive protein [8], presence of richly vascularized fibrous tissue [2], and elevated numbers of the tumor necrosis factor-immunoreactive cells in the intervertebral disc [7] have been identified in the end plates and blood of patients with Modic 1 changes.

Back pain with lumbar extension was also independently and strongly associated with Modic 1 lesions. Moreover, the presence of lateralized clinical pain was associated with lateralized inflammatory Modic 1 signals in the same side. Kjaer et al. [5] described more intense pain with lumbar movement for patients with Modic changes than patients with common LBP, but did not differentiate between flexion and extension. Maigne et al. [19] described an association of inflammatory pain characteristics and pain with lumbar extension as well as frequent presence (but not in all patients) of Modic changes for these patients when MRI results were available in patients exhibiting a positive response to a short course of oral corticosteroids. There is no clear explanation for this clinical fact. The closure of the intervertebral foramen accompanying extension would be relevant only in cases with radicular pain. Our hypothesis was that pain in extension could be a marked feature only in patients with a dorsal localization of the changes within the disc and the adjacent endplates. Extension would have crushed the inflammatory zone, eliciting pain. This proved untrue, as cases with ventral localization exhibited the same feature.

Mechanical stress was suggested as one of the possible causes of Modic 1 changes [6] because of a strong association of inflammatory changes, severely degenerated discs and previous disc herniation. Our findings of pain on the same side as inflammatory changes seen on MRI, exacerbated pain during back extension and sedentary work as a protective factor can highlight this hypothesis. Starting from this theory, rest therapy (load reduction and daily rest) has been proposed for patients with Modic 1 changes, but does not seem effective [20].

Finding conservative therapies for LBP is a challenge because of its heterogeneous pathophysiological mechanism. The identification of subgroups of patients with LBP should help in the search for specific therapeutics. Modic 1 changes could define a well characterized subgroup of patients with inflammatory pain and increased pain with hyperextension. In this study corticosteroids had a better effect than NSAIDs and no side effects were reported where short course treatments were used (2–3 weeks maximum), but neither the dose nor the route of administration was specifically studied. Although corticosteroids are not recommended by the European guidelines for non-specific LBP, some studies have reported a positive effect of corticosteroids in patients with Modic 1 [19, 21, 22]. Randomized trial and long-term follow-up are needed to determine the magnitude of the effect and impact of side effects before this treatment can be recommended.

Our study has some limitations. Presence of back pain and inflammatory signals on MRI could suggest spondyloarthritis, but we took care to exclude these patients; however, no validated criteria were recorded. Patients with spondyloarthropathy were excluded mainly from clinical characteristics, according to the criteria published by the ASAS group [23]. As recommended, MRI of the SI joint was ordered in case of doubt. All the clinicians involved in this study are rheumatologists with a special interest in back pain, and are members of the spine section of the French Society of Rheumatology. Also, a recent study revealed that patients with Modic 1 changes did not fulfill validated criteria for ankylosing spondylitis [24].

In conclusion, this study gives evidence of a specific pain pattern, with inflammatory characteristics, associated with Modic 1 changes in patients with LBP. More studies are needed to confirm these results and evaluate therapies for patients with Modic 1 changes.

Conflict of interest None.

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