Assessment of Ankylosing Spondylitis Criteria in Patients with Chronic Low Back Pain and Vertebral Endplate Modic I Signal Changes

CHRISTELLE NGUYEN, IMAD BENDEDDOUCHE, KATHERINE SANCHEZ, MARYLÈNE JOUSSE, AGATHE PAPELARD, ANTOINE FEYDY, MICHEL REVEL, SERGE POIRAUDEAU, and FRANÇOIS RANNOU

ABSTRACT. ***Objective.*** Patients with chronic low back pain (cLBP) and vertebral endplate Modic I signal changes on lumbar magnetic resonance imaging (MRI) have clinical features that could mimic inflammatory back pain related to spondyloarthritis (SpA) and/or ankylosing spondylitis (AS). We aimed to assess whether such patients fulfilled criteria for SpA and/or AS.

Methods. For 5 months in 2008, all patients (n = 314) referred to a tertiary care physical medicine and rehabilitation facility in France were consecutively screened. A total of 185 hospitalized for nonspecific cLBP were prospectively assessed. Forty patients fulfilling inclusion criteria were consecutively enrolled and included in 2 groups according to MRI findings: Modic I (n = 15) and non-Modic I (n = 25). MRI findings were assessed independently by 2 spine specialists and a radiologist. HLA-B27 status was determined. Data were collected on clinical measurements and fulfillment of Amor criteria (AC) and modified New York criteria (mNYC). All assessors were blinded to HLA-B27 status.

Results. Whatever the Modic group, no patient fulfilled AC or mNYC, and mean total scores were comparable [3 ± 2 (range 0–22; p = 0.977), 1 ± 1 (range 0–3; p = 1.000), and 0 ± 0 (range 0–1; p = 1.000) for AC and clinical and radiological mNYC, respectively]. HLA-B27 status was similar in both groups [n = 2 (13%) vs n = 0 (0%); p = 0.135].

Conclusion. Patients with cLBP and Modic I vertebral endplate signal changes on lumbar MRI do not fulfill widely used and validated criteria for SpA and/or AS. Such cases are clinically distinct from SpA and AS. (J Rheumatol First Release August 15 2010; doi:10.3899/jrheum.100165)

Key Indexing Terms:
CHRONIC LOW BACK PAIN HLA-B27 MODIC VERTEBRAL ENDPLATE SIGNAL
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Using magnetic resonance imaging (MRI), de Roos, *et al*[1] and Modic, *et al*[2] described modifications of the vertebral endplate marrow signal anecdotally present in asymptomatic populations but significantly associated with chronic low back pain (cLBP)[3,4,5]. Modic I signal changes correspond to vertebral body edema, while Modic II signal changes reflect fatty degeneration. Recent findings suggest that Modic I signal changes may be related to local inflammation, along with low-grade systemic inflammation: biopsy samples have shown replacement of marrow by richly vascularized fibrous tissue[2], increased levels of interleukin 6[6], and a higher number of tumor necrosis factor (TNF) immunoreactive cells[7] in the intervertebral disc. In addition, patients with Modic I changes have been reported to display a particular clinical and biological profile: longer duration of morning stiffness, more frequent late night and morning pain, and higher levels of serum high-sensitivity C-reactive protein[8]. This clinical and biological inflammatory profile, along with the lack of specificity of isolated spinal inflammatory lesions detected by MRI[9,10], brings into question the pathogenic mechanisms underlying Modic changes; some authors hypothesize mechanical, infectious, or inflammatory causes[11,12]. Therefore, the differential diagnosis with other etiologies of inflammatory cLBP, especially ankylosing spondylitis (AS) and spondyloarthritis (SpA), can be particularly challenging. The main challenge is to deliver biologic treatment only to patients with AS and SpA and not to all the patients with cLBP who have inflammatory Modic I lesions seen on MRI.

Our aim was to assess whether patients with cLBP and vertebral endplate Modic I signal changes diagnosed on

From the Paris Descartes University; Department of Rehabilitation and Department of Radiology B, Cochin Hospital, Assistance Publique-Hôpitaux de Paris; and INSERM, Institut Fédératif de Recherche sur le Handicap, Paris, France.

C. Nguyen, MD; I. Bendeddouche, MD; K. Sanchez, MD; M. Jousse, MD; A. Papelard, MD; M. Revel, MD; S. Poiraudeau, MD, PhD; F. Rannou, MD, PhD, Paris Descartes University; Department of Rehabilitation, Cochin Hospital, APHP; INSERM, Institut Fédératif de Recherche sur le Handicap; A. Feydy, MD, PhD, Paris Descartes University, Department of Radiology B, Cochin Hospital, AP-HP.

Address correspondence to Prof. F. Rannou, Department of Rehabilitation, Cochin Hospital, 27 Rue du Faubourg Saint-Jacques, 75014 Paris, France. E-mail: francois.rannou@cch.aphp.fr

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lumbar MRI fulfilled clinical and/or biological criteria for AS and SpA.

MATERIALS AND METHODS

Patient selection. From April to September 2008, inpatients (n = 314) referred to our department were consecutively screened, and those with cLBP were prospectively assessed. Inclusion was based on fulfillment of the following criteria: severe nonspecific cLBP, defined as LBP persisting for more than 3 months, with no response to 3-month conservative treatment and severe interference with lifestyle; age ≥ 18 years; and MRI of the lumbar spine performed in the last 6 months. Exclusion criteria were having undergone back surgery; LBP related to known AS and/or SpA, infection, tumor, or fracture; and presence of predominant radiculalgia (Figure 1).

Clinical characteristics. Three assessors, who were blinded to the HLA-B27 status of each patient, recorded data on age at the time of evaluation, sex, weight, height, occupation, sick leave duration, duration of symptoms, LBP intensity on a visual analog scale (VAS; 0–100 mm), handicap on a VAS (0–100 mm), Quebec disability score (20 items, scored from 0 = no disability to 5 = impossible to do; range of final score 0–100), presence and duration of morning stiffness (min), 24-hour worst painful moment, thoracic expansion (cm), and lumbar flexibility (modified Schöber and finger-to-floor tests, cm). Finally, clinical evaluation included Amor classification criteria (AC) for SpA[13] (range 0–22, cutoff for positivity = 6) and clinical and radiological modified New York criteria for AS[14] (mNYC, range 0–3 and 0–1 for clinical and radiological mNYC, respectively). Three criteria sets for inflammatory back pain (IBP) were applied to the collected data, namely 1977 Calin criteria[15], 2006 Berlin criteria[16], and 2009 Assessment of SpondyloArthritis international Society (ASAS) criteria[17]. Calin criteria refer to IBP criteria by Calin, *et al*[15], which are fulfilled if at least 4 of the following 5 conditions are present: (1) age at onset < 45 years; (2) back pain > 3 months; (3) insidious onset; (4) associated with morning stiffness; and (5) improvement with exercise. Berlin criteria refer to IBP criteria by Rudwaleit, *et al*[16], which are fulfilled if at least 2 of the following 4 conditions are present: (1) morning stiffness > 30 min; (2) improvement with exercise but not with rest; (3) awakening in the second half of the night because of back pain; and (4) alternating buttock pain. ASAS criteria refer to IBP criteria by Sieper, *et al*[17], which are fulfilled if at least 4 of the following 5 conditions are present: (1) improvement with exercise; (2) pain at night; (3) insidious onset; (4) age at onset < 40 years; and (5) no improvement with rest. All patients underwent anteroposterior radiography of the pelvis for scoring of the sacroiliac joint radiographs according to mNYC.

HLA-B27 status. HLA typing was performed in one laboratory (Saint Louis Hospital, Department of Immunology and Histocompatibility, Paris), with blinding to the MRI evaluation and clinical characteristics of each patient.

Lumbar MRI evaluation. MR images were assessed independently by 2 spine specialists and a radiologist with experience in spine MRI, who were blinded to the HLA-B27 status. The reviewers graded the endplate marrow signal changes of the 5 lumbar discs. The signal changes in endplate marrow indicated ≥ 50% anteroposterior edema in the Modic I group and no signal changes or ≥ 50% anteroposterior fatty deposits or < 50% anteroposterior edema in the non-Modic I control group.

This survey was conducted in compliance with the Good Clinical Practices protocol and the Declaration of Helsinki principles. In accord with French national law, formal approval from an ethical committee is not required for this kind of project. All patients gave their consent to participate after being informed about the study protocol.

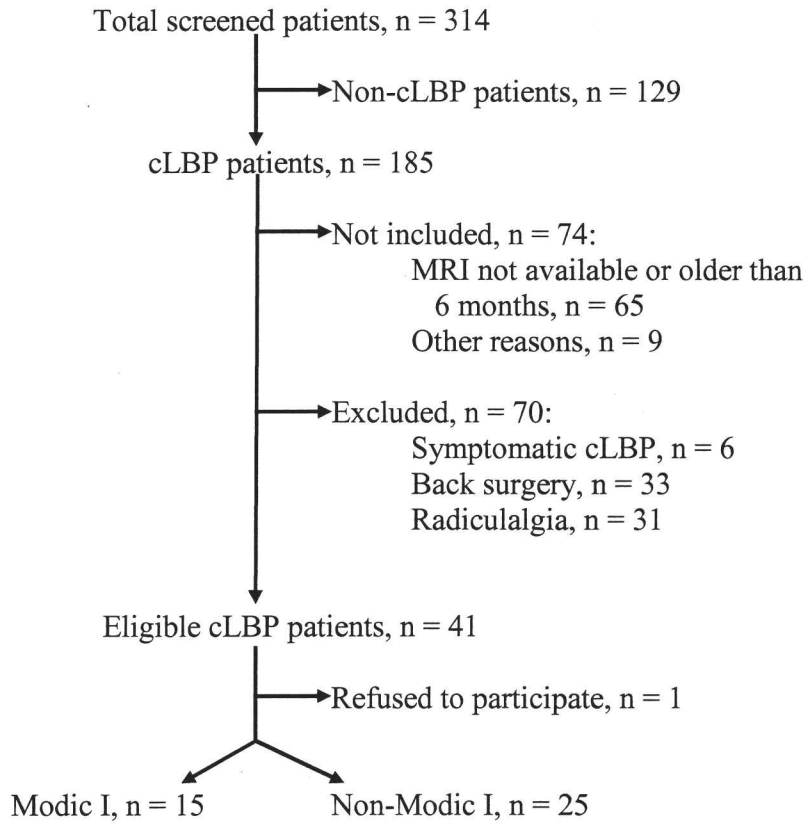

Figure 1. Total number of patients with chronic low back pain (cLBP) screened from April to September 2008 and exclusion criteria. MRI: magnetic resonance imaging.

Statistical analysis. Data analysis involved use of Systat v9 (Systat, Chicago, IL, USA). Qualitative data were described with percentages and quantitative data with means ± SD. We compared the biological and clinical measurements between the 2 groups. Quantitative variables were compared by the nonparametric Kruskal-Wallis test and qualitative variables by Fisher's exact test. A $p < 0.05$ was considered statistically significant.

RESULTS

A total of 314 patients were prospectively screened. Of these, 129 patients were hospitalized for reasons other than disabling cLBP. Among the 185 patients hospitalized for cLBP, 74 were not included because of absence of MRI results or MRI results older than 6 months (n = 65) or for other reasons (n = 9); 70 patients were excluded because of previous back surgery (n = 33), predominant radiculalgia (n = 31), or symptomatic cLBP (n = 6). Among the 41 remaining eligible patients, 1 refused to participate in the survey. Overall, 40 patients (13 men) were consecutively enrolled in the Modic I (n = 15) or non-Modic I control group (n = 25; Figure 1).

Description of patients. According to vertebral endplate Modic signal changes, the 2 Modic groups were similar for all the assessed baseline characteristics: age, sex, duration of symptoms, body mass index, occupation, LBP intensity, handicap, and level of disability (Table 1).

Imaging findings. In the Modic I group, signal changes involved a single lumbar level in each case: L5/S1 in 6 patients, L4/L5 in 4, L3/L4 in 2, L2/L4 in 2, and L1/L2 in 1. No other inflammatory lesions were identified in this group (neither Romanus nor inflammatory zygapophyseal changes). In the non-Modic I control group, Modic 0 signal changes were observed in 22 patients and Modic II signal changes in 3 patients. Vertebral endplate signal changes including magnetic Romanus and inflammatory zygapophyseal changes were absent. Whatever the group of patients, no fatty signal changes at the vertebral corner were detected. Degenerative spinal lesions without inflammatory findings, including facet joint osteoarthritis, and involving several lumbar levels, were identified in most of the cases.

Inflammatory features and physical characteristics. According to vertebral endplate Modic signal changes, the 2 Modic groups were similar in assessed inflammatory features: presence and duration of morning stiffness and worst painful moment (Table 2). Overall, 8 (53.3%), 5 (43.3%), and 6 (40%) patients fulfilled Calin, Berlin, and ASAS criteria in the Modic I group, respectively, and 12 (48%), 8 (32%), and 9 (36%) patients fulfilled Calin, Berlin, and ASAS criteria in the non-Modic I control group, with no significant differences between the 2 groups. Duration of morning stiffness was longer and the worst painful moment during late night and morning was more frequent for the Modic I than the non-Modic I group, but not significantly (133 ± 364 vs 31 ± 49 min, respectively, $p = 0.181$; and 40% vs 24%, $p = 0.311$). Finally, the 2 groups were comparable in thoracic expansion and lumbar flexibility assessed by modified Schöber test and finger-to-floor test (Table 2).

Criteria for SpA and AS. Whatever the group considered, AC and mNYC were not fulfilled, and mean total scores were comparable [3 ± 2, range 0–22 ($p = 0.977$), 1 ± 1, range 0–3 ($p = 1.000$), and 0 ± 0, range 0–1 ($p = 1.000$) for AC and clinical and radiological mNYC, respectively]. Radiographs of sacroiliac joints demonstrated the absence of sacroiliitis in all patients with cLBP (Table 3).

HLA-B27 status. Histocompatibility typing performed for the 40 included patients showed presence of HLA-B27 in 2 patients in the Modic I group. The 2 groups did not differ in HLA-B27 status ($p = 0.135$; Table 3).

DISCUSSION

Previous studies assessing patients with vertebral endplate Modic I signal changes have suggested that such patients could share common features of patients with inflammatory cLBP related to AS and/or SpA[8]. In our study, patients with cLBP who had vertebral endplate Modic I signal changes did not fulfill clinical, biological, or imaging criteria for AS and/or SpA. These patients seemed to show more inflammatory features, including longer duration of morning stiff-

Table 1. Characteristics of patients with chronic low back pain, by vertebral endplate marrow Modic signal changes on magnetic resonance imaging. Values are the mean ± SD unless otherwise indicated.

Characteristics	All Patients, n = 40	Modic I, n = 15	Non-Modic I, n = 25	p*
Age, yrs	49 ± 11	53 ± 12	46 ± 9	0.159
Age < 50 years, n (%)	21 (52.5)	6 (40)	15 (60)	0.220
Women, n (%)	27 (67.5)	9 (60)	18 (72)	0.498
Symptom duration, yrs	9 ± 11	12 ± 14	6 ± 8	0.082
BMI, kg/m^2	28 ± 5	27 ± 5	28 ± 5	0.635
Retirement, n (%)	3 (7.5)	2 (13)	1 (4)	0.545
Pain, 100-mm VAS	53 ± 22	46 ± 23	57 ± 22	0.111
Handicap, 100-mm VAS	62 ± 18	60 ± 21	64 ± 17	0.625
Quebec Disability Score (range 0–100)	48 ± 14	43 ± 14	51 ± 13	0.150

* Nonparametric Kruskal-Wallis test or Fisher's exact test; $p < 0.05$. VAS: visual analog scale; BMI: body mass index.

Table 2. Inflammatory features and physical characteristics of patients with chronic low back pain, by vertebral endplate marrow Modic signal changes on magnetic resonance imaging. Values are the mean ± SD unless otherwise indicated.

Features	All Patients, n = 40	Modic I, n = 15	Non-Modic I, n = 25	p*
Inflammatory back pain criteria sets				
Calin criteria[15], n (%)	20 (50.0)	8 (53.3)	12 (48.0)	0.744
Berlin criteria[16], n (%)	13 (32.5)	5 (33.3)	8 (32.0)	0.931
ASAS criteria[17], n (%)	15 (37.5)	6 (40.0)	9 (36.0)	0.800
Presence of morning stiffness, n (%)	17 (42.5)	8 (53.3)	9 (36.0)	0.336
Morning stiffness, min	69 ± 227	133 ± 364	31 ± 49	0.181
Worst painful moment during late night and morning, n (%)	13 (30)	6 (40)	6 (24)	0.311
Thoracic ampliation, cm	6 ± 2	7 ± 2	6 ± 2	0.142
Modified Schober test, cm	20 ± 1	19 ± 2	20 ± 1	0.654
Finger-to-floor test, cm	23 ± 16	25 ± 17	22 ± 16	0.068

* Nonparametric Kruskal-Wallis test or Fisher's exact test; $p < 0.05$. ASAS: Assessment of SpondyloArthritis international Society.

Table 3. Ankylosing spondylitis criteria for patients with chronic low back pain, by vertebral endplate marrow Modic signal changes on magnetic resonance imaging. Values are mean ± SD unless otherwise indicated.

Criteria	All Patients, n = 40	Modic I, n = 15	Non-Modic I, n = 25	p*
Amor (range 0–22 points)	3 ± 2	3 ± 2	3 ± 2	0.977
New York clinical (range 0–3)	1 ± 1	1 ± 1	1 ± 1	1.000
New York radiological (range 0–1)	0 ± 0	0 ± 0	0 ± 0	1.000
HLA-B27-positive, n (%)	2 (5)	2 (13)	0 (0)	0.135

* Nonparametric Kruskal-Wallis test or Fisher's exact test; $p < 0.05$.

ness and more frequent "worst painful moment" during late night and morning than did patients with cLBP who had non-Modic I signal changes, as reported[8]. When applying criteria sets designed for IBP, namely Calin, Berlin, and ASAS, no differences were found between Modic I and non-Modic I patients. Further, whatever the Modic group, mNYC and AC were never fulfilled, with no sacroiliitis seen on radiography. Our findings indicate that patients with cLBP who had Modic I signal changes do not fulfill the current most commonly used diagnostic criteria and screening tools for AS or SpA.

Among patients in the Modic I group (n = 15), 2 (13%) were positive for HLA-B27: a 48-year-old man and a 61-year-old woman. On closer examination of their files, neither fulfilled mNYC, but for both, the total score was 5, with fulfillment of 3 of 11 AC, including night pain, heel pain, buttock pain for one, and family history for the other. Results are lacking of prospective surveys investigating the predictive value of the association of Modic I lesions, HLA-B27 positivity, and absence of radiographic evidence of sacroiliitis in the diagnosis of AS. In contrast, much data support the great utility of sacroiliac joint MRI for early diagnosis of AS in the preradiographic stage[18,19].

Considering other clinical characteristics of Modic I patients, our findings are consistent with published data: duration of morning stiffness was longer and the worst painful moment during late night and morning was more frequent, although not significantly, in the Modic I group than in the non-Modic I group[8]. The absence of statistical significance between Modic I and non-Modic I control groups for these 2 criteria may be explained by the heterogeneity of the non-Modic I control group (because this group included patients with cLBP with both Modic 0 and Modic II changes), and by the small sample size. For the first time, various criteria sets for IBP were tested in patients with cLBP who had Modic I vertebral endplate signal changes. Compared to patients with cLBP who were non-Modic I, patients with cLBP who were Modic I more often met Calin, Berlin, or ASAS criteria for IBP, although not significantly. Even though these criteria sets were first designed to clinically differentiate back pain caused by inflammation of the sacroiliac joints/lower spine from other causes related to AS, we found that a high percentage of patients with cLBP who were Modic I may exhibit IBP symptoms, without meeting AC or mNYC. Our findings indicate that the specificity of these criteria may be lowered in this particular subgroup of patients with cLBP.

Ensuring the absence of AS or SpA criteria in patients with cLBP with vertebral endplate Modic I signal changes is crucial to allow for early and reliable diagnosis and to avoid

inadequate treatment. Although nonsteroidal antiinflammatory drugs and TNF blockers have had good efficacy in the treatment of AS[20], Modic I patients may benefit from intradiscal steroid injection[21]. Recently, intradiscal injections of corticosteroids have been reported to be more effective for patients with cLBP who have Modic I vertebral endplate signal changes[21]. Further, lumbar arthrodesis for patients with degenerative disc disease has shown good results for those with Modic I signal changes, because lumbar arthrodesis accelerates the course of Modic I lesions and leads more rapidly to Modic II lesions, which are less inflammatory and less painful[4,5,7,21,22].

Our study has several limitations. Our sample size was small, and a more extensive prospective study is required to confirm the lack of relation between Modic I changes and positivity for AS or SpA assessment criteria for patients with cLBP. Another limitation may be the procedure used to recruit patients. All selected patients were recruited from a tertiary care unit specializing in spinal disorders, so they may not be representative of the whole French cLBP primary care population. Thus, the proportion of Modic I patients with cLBP in our study population (37.5%) is higher than that described in previous studies of cLBP with or without radiculalgia, which varied from 4% to 29%[2,22]. In addition, patients showed long symptom duration at inclusion, which did not allow assessment of characteristics of patients with recent LBP and Modic I signal changes. Another limitation was the chosen classification criteria sets for AS and SpA themselves. For example, although bilateral sacroiliitis of grade 2 or unilateral sacroiliitis of grade 3 or higher, shown by radiographic examination, is still mandatory to meet mNYC, neither the sensitivity nor the specificity of radiographically seen sacroiliitis can be considered higher than about 80%[23]. Actually, classification criteria ensure the optimal differentiation of a specific rheumatic disease from another group of diseases for purposes of clinical or epidemiological research. Classification criteria differ from diagnostic criteria, which are designed to assist clinicians in establishing a diagnosis under the conditions of daily practice. However, most of the criteria initially developed for the classification of rheumatic diseases are widely used as diagnostic criteria. Examples include the criteria for SpA and AS. The mNYC are classification criteria for AS, which are also used for diagnostic purposes, while AC are classification criteria for SpA. The AC are broader than the mNYC. However, as AC and mNYC were intended for purposes of classification, they may lack sensitivity for establishing the early diagnosis of AS and SpA[24].

Patients with cLBP who have Modic I lesions do not fulfill widely used and validated criteria for AS or SpA. Our findings suggest that isolated inflammatory vertebral endplate changes involving the lumbar spine, without radiographic evidence of sacroiliitis, in the cLBP population are not associated with AS or SpA. However, a prospective survey could be performed of patients with cLBP who have isolated inflammatory vertebral endplate changes involving the lumbar spine and who do not have radiographic evidence of sacroiliitis, but are HLA-B27-positive. It is more likely that cLBP associated with lumbar Modic I signal changes is a clinical entity distinct from AS. Therefore, ensuring the absence of AS criteria in this subgroup of patients with cLBP is mandatory to avoid misdiagnosis and is of therapeutic interest because the efficacy of specific therapies has been suggested.

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