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Original article

Can we improve the diagnosis of spondyloarthritis in patients with uncertain diagnosis? The EchoSpA prospective multicenter French cohort

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ABSTRACT

Power Doppler ultrasound (PDUS) has proved to be a highly sensitive tool for assessing enthesitis in spondyloarthritis (SpA). In patients with a suspected SpA, diagnosis could be improved by detecting enthesitis with PDUS.

Objective: To evaluate the performance of PDUS for the diagnosis of SpA alone or combined with other clinical, laboratory and imaging findings in patients consulting for a suspected SpA.

Methods: Prospective, multicenter French cohort study (Boulogne-Billancourt, Brest, Caen, Grenoble, Marseille and Nancy). Outpatients consulting for symptoms suggestive of SpA (inflammatory back pain [IBP], arthritis or inflammatory arthralgia [IA], enthesitis or dactylitis [ED], HLA-B27 positive uveitis [B27+U], familiarity for SpA [Fam]) were recruited and followed up for at least 2 years. Sample size was set to 500 patients (for estimated prevalence of SpA of 30 ± 5% after 2 years). At baseline, patients were submitted to standardized physical examination, pelvic X-ray, sacroiliac joints magnetic resonance imaging (MRI), HLA-B typing, and other tests judged useful for diagnosis. For each patient, a blinded PDUS examination of 14 enthesitic sites was performed at baseline and at years 1 and 2. Patients were planned to be followed during 5 years. The diagnosis of SpA ascertained by an experts' committee, blind to PDUS results, after at least 2 years of follow-up, with a revaluation of doubtful patients at 5 years will be used as gold standard for evaluating the diagnostic performance of PDUS and the best diagnostic procedure by combining PDUS, clinical symptoms and other tests.

Results: Between January 2005 and September 2007, 489 patients were included (96% of the target population). Nineteen patients (0.2%) retired their informed consensus or were lost to follow-up immediately after their inclusion. At baseline, mean age of the 470 remaining patients was 40 years, mean duration of symptoms was 6.1 years; 42% of them were HLA-B27+ and 63% were female. Primary inclusion criterion was IBP in 53%, IA in 27%, ED in 9%, B27+U in 8% and Fam in 4%. Follow-up is still ongoing.

Conclusion: We have set up a unique diagnostic cohort which includes the entire spectrum of SpA manifestations. By using PDUS we expected to improve the diagnostic procedure of SpA.

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The spondyloarthritis (SpA) are a group of inflammatory rheumatic disorders comprising ankylosing spondylitis (AS), the most common phenotype, psoriatic arthritis and spondylitis, reactive arthritis, arthritis with inflammatory bowel disease (Crohn's disease or ulcerative colitis), and undifferentiated SpA. With a prevalence of 0.3–0.5%, SpA are the second most frequent inflammatory rheumatic disorders [1]. Increased frequency of HLA-B27, familial aggregation and axial skeleton involvement are characteristics of these disorders. The unified lesions belonging to all SpA subtypes is the inflammation at the insertion of ligaments, tendons or joint capsules into bone, which is termed enthesitis [2]. Recently, the importance of peripheral enthesitis among SpA manifestations has been emphasized by several authors and is best reflected by its inclusion as a classification criterion for SpA [3–5]. However there are no definite clinical criteria for the diagnosis of this manifestation and symptomatic findings such as localized pain, tenderness, and swelling lack of specificity [6–8]. For those reasons, the use of imaging technique is helpful in clinical daily practice [9,10].

Because SpA starts relatively early in life and has a chronic progressive course, the impact of the disease on health resources is important. One major hurdle faced by clinicians remains their inability to establish an early diagnosis because of the poor specificity of symptoms revealing SpA [9]. The mean duration of symptoms between the first manifestation and the diagnosis has been reported to last being between 7 and 9 years [11]. Several classification criteria sets have been developed to help clinician for recognising SpA. Some criteria sets embrace the entire SpA spectrum, such as the Amor's, and the European Spondylarthropathy Study Group (ESSG) criteria [4,5]. Others are limited to definite axial forms (i.e. modified New York criteria) [12]. Nevertheless neither set is satisfying for diagnosing early SpA [13,14]. At the beginning of the disease, when criteria for definite forms are often not met, the use of imaging technique such as magnetic resonance imaging (MRI) or ultrasound might help to demonstrate the inflammation of involved structures. Because the axial inflammation detected by MRI was demonstrated to be predictive of the future development of radiographic sacroiliitis [15–20], this sign was included in the most recent classification criteria set developed for axial SpA: the Assessment of SpondyloArthritis international Society (ASAS) criteria [21]. However the sensitivity of the technique in such cohort was estimated to be around 60%. Moreover several patients never present axial symptoms. For helping to identify those patients, ASAS proposed a set of criteria based on the objective evaluation of a peripheral involvement (by clinic or imaging techniques) and the concomitant presence of other specific manifestations [22]. Among the different imaging techniques which can be used for evaluating joint and tendon involvement, ultrasound, both in grey-scale and in power Doppler, appears as an economic and objective tool [23,24]. Its applicability to several joints and its dynamic evaluation of structures has permitted to this technique to become a natural prolongation of the physical examination [25,26].

Several studies have described the grey-scale aspect of lower limbs enthesitis in SpA, revealing the high frequency of asymptomatic ultrasound abnormal findings [27]. In these studies, the high prevalence of peripheral entheseal abnormalities detected outlines the primary significance of this finding among SpA manifestations. It was demonstrated that the accuracy of the peripheral enthesitis detection in SpA patients can be improved by using together grey-scale and power Doppler (PDUS) [27–29]. The landmark of PDUS enthesitis can be considered an abnormal vascularization of the enthesis, which seems exclusively detected in SpA patients irrespectively of phenotype [30], and which may permit to diagnose SpA in suspected patients [31]. Considering those promising data and in order to confirm the performance of PDUS for diagnosing SpA, we set out a multicenter French cohort of patients consulting for symptoms suggestive of SpA. Our primary objective is to evaluate the capability of PDUS to diagnose SpA. Our secondary objective is to establish the best diagnostic strategy for SpA, by combining PDUS, MRI of sacroiliac joints, clinical presentation and the other diagnostic procedures included in the protocol.

1. Methods

1.1. Study design

This is a French multicentre, prospective, cohort study (2 years of enrolment and 5 years of follow-up). Outpatients consecutively referred to six rheumatology departments (Boulogne-Billancourt, Brest, Caen, Grenoble, Marseille and Nancy) for symptoms suggestive of SpA, without any definite diagnosis, were considered eligible to be enrolled in this study. The six centers were selected based on the experience of investigators in conducting longitudinal epidemiological or therapeutic studies and according to their ability to perform a PDUS examination of entheses.

Patients were proposed to be included if they presented the following criteria: (a) inflammatory back pain (IBP), (b) arthritis or inflammatory arthralgia, (c) peripheral enthesitis or dactylitis, (d) uveitis associated with the presence of HLA-B27; (e) familiarity for SpA and suggestive symptoms. For IBP, arthritis, arthralgia, and enthesitis, symptom duration greater than 3 months and age less than 50 years were required. IBP was defined according to Calin criteria [5], or by the presence of night awakenings and morning stiffness greater than 1 hour and/or improved by exercise [32]. Inflammatory arthralgia was defined as painful joint, responsible for night awakening, and/or morning stiffness greater than 1 hour, without synovitis on examination. In patients with several inclusion criteria, the most prominent one was considered as primary. Patients were not included if they were aged less than 18 years, if a definite diagnosis of AS, or other well-defined disease accounting for the presenting manifestation(s) had been made during the eligibility visit, if they expected to move from the inclusion center area during the 2 years following the inclusion, or if they presented any contraindication to MRI.

Protocol was approved by the institutional ethics committee of the hospital of coordinating center (Boulogne-Billancourt) and is registered in the clinical trials registry (http://clinicaltrials.gov/) under the number of NCT00794404. Before inclusion, all patients gave a written informed consent to participate.

1.2. Patient recruitment

Recruitment was performed in close connection with local community rheumatologists. Each center acted as an observational center and did not interfere with patient treatment and diagnosis. Patients were planned to be followed up into the cohort for at least 2 years, with an annual physical examination. Then they were asked to continue the study up to 5 years of follow-up. During this period of time, the management of the patients was under the supervision of the rheumatologist who referred the patient to the cohort. Referring rheumatologist was asked every 6 months whether a definite diagnosis was ascertained.

1.3. Assessment

1.3.1. Patient evaluation and follow-up

In each center, at baseline and at each visit (years 1, 2, and 5), all patients were submitted to a standardized physical examination by a qualified rheumatologist, blinded to the diagnosis suspected by the referral rheumatologist. At this first visit all exams included in the protocol were prescribed: PDUS of entheses, MRI of sacroiliac joints and of the other most painful site if present; conventional radiograph of pelvis, and of the other involved joints, as well as all