


High Prevalence of Undiagnosed Axial Spondyloarthritis in Patients with Chronic Low Back Pain Consulting Non-Rheumatologist Specialists in Belgium: SUSPECT Study

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ABSTRACT

Introduction: Diagnosis of axial spondyloarthritis (SpA) can be delayed for several years mainly because of low awareness of axial SpA among non-rheumatologists who are the first interlocutors of potential SpA patients. One strategy to decrease the delay between appearance of first symptoms and diagnosis of axial SpA and to allow early management of the disease is to provide the non-rheumatologists with tools to identify patients requiring prompt referral to rheumatologists. This study was designed to evaluate in a real-world setting

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whether screening patients with chronic low back pain who consult physical medicine and rehabilitation (PMR) physicians, orthopedists, and ophthalmologists is useful in detecting axial SpA.

Methods: During this non-interventional cross-sectional study, data from 161 patients with chronic back pain, consulting an orthopedist, PMR physician, or ophthalmologist were collected during a single visit. Any patient who presented with at least four out of five symptoms of inflammatory back pain (IBP) and at least one additional SpA feature were to be referred to a rheumatologist. Analysis was purely descriptive.

Results: IBP was diagnosed in approximately half of the patients (89 patients) and 72 of them met the referral criteria. A total of 117 patients were finally referred to a rheumatologist and axial SpA was diagnosed for 37 of them.

Conclusions: The high prevalence of undiagnosed axial SpA in patients with chronic back pain visiting PMR physicians, orthopedists, and ophthalmologists suggests that these healthcare professionals may play a key role in the strategy developed to shorten the delay observed in the formal diagnosis of SpA.

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Keywords: ASAS criteria; Inflammatory back pain; Ophthalmologist; Orthopedists; Physical medicine and rehabilitation physician; Referral

INTRODUCTION

Low back pain has been reported to affect 60–70% of adults during their lifetime and is a regular cause for seeking medical care [1, 2]. Low back pain is defined as chronic if symptoms persist for more than 3 months. Although chronic low back pain is most often degenerative, in about 5% of patients, the pain results from inflammation [3, 4] and is referred to as inflammatory back pain (IBP). One of the causes of IBP is axial spondyloarthritis (SpA), of which the prevalence is approximately 0.5–1% in the general population [5–8]. Chronic IBP has been identified as a major clinical feature of SpA and is experienced by most patients, whereas other peripheral or extra-articular manifestations (inflammation of peripheral joints with asymmetrical arthritis, predominantly of the lower limb; occurrence of enthesitis; uveitis) are present in approximately 40–60% of patients [6]. Axial SpA refers to patients with predominant axial involvement and axial complaints, and includes both ankylosing spondylitis (AS), for which evidence of sacroiliitis (another hallmark of SpA) is detected on X-rays, and non-radiographic axial SpA, where sacroiliitis is visible via magnetic resonance imaging (MRI) but not on X-rays [6]. Evidence has been gathered that non-radiographic axial SpA might be an early stage of AS, although not all cases of axial SpA will progress to AS [9, 10]. A strong association with Human Leucocyte Antigen-B27 (HLA-B27) has also been evidenced [11] and can be considered as the third main clinical feature of axial SpA.

Based on these observations, over the past seven decades, several criteria and algorithms have been developed for the classification of AS and axial SpA. In 2009, the Assessment of SpondyloArthritis International Society (ASAS) released a new set of criteria for SpA in patients with chronic back pain [12–14]. The definition of IBP has been revised [15]. Sacroiliitis on imaging (X-rays or MRI) is the main criteria for the imaging arm, whilst the presence of HLA-B27 is the main criteria for the clinical arm. The ASAS criteria are met if at least one (in the imaging arm) or two (in the clinical arm) other SpA features are present [IBP, arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn's disease/ulcerative colitis, good response to nonsteroidal anti-inflammatory drugs (NSAIDs), family history of SpA, HLA-B27 and elevated C-reactive protein (CRP)] [12]. Although these criteria are intended for classification, they could also be a useful referral tool in the primary healthcare setting, allowing non-rheumatologists to determine whether referral to a rheumatologist is necessary.

Axial SpA has an early onset (generally in the second or third decade of life), which may hinder early diagnosis, as younger individuals may be less likely to promptly consult with a rheumatologist. These individuals may first turn to general practitioners or physical medicine and rehabilitation (PMR) physicians who are often the first interlocutors of potential patients with SpA. Non-rheumatologist specialists such as ophthalmologists and orthopedists are also consulted when extra-articular manifestations of the disease occur (for instance, uveitis or dactylitis) [16]. It is generally admitted that there is a delay of 5–10 years from the onset of symptoms (generally stiffness and axial pain) to a final diagnosis of AS [11, 14, 16]. On the other hand,

efficient treatment strategies, such as NSAIDs, and more recently tumor necrosis factor (TNF) blockers, are available and seem to be most effective in the early stages of the disease [15]. Signs and symptoms associated with axial SpA (nocturnal pain, morning stiffness, fatigue, limitation of spinal mobility and ultimately ankylosis with disease progression) as well as symptoms associated with peripheral involvement, might seriously impact patient quality of life and have a non-negligible cost for society [17]. Facilitating an early diagnosis is therefore among the objectives clearly identified by ASAS to improve patient well-being [14, 18]. Some studies have highlighted the lack of awareness among general practitioners, especially regarding the disease spectrum and early detection [3, 19]. One strategy to shorten the delay between the occurrence of first symptoms and the final diagnosis of AS is to increase the awareness of SpA and AS among primary healthcare professionals and non-rheumatologist specialists, providing them with tools to identify these patients among the large population of patients with back pain. Recently, several referral strategies, mostly intended for general practitioners and primary care professionals, have been developed to allow earlier diagnosis [2, 10, 20, 21]. The SUSPECT study was designed to evaluate whether real-life screening of patients with chronic back pain who consult PMR physicians, orthopedists, and ophthalmologists is useful in detecting axial SpA.

METHODS

Protocol Overview and Study Design

The SUSPECT study was approved by the ethics committee of Erasme Hospital (Brussels, Belgium) and conducted according to local

regulations. It has therefore been performed in accordance with the ethical standard laid down in the 1964 Declaration of Helsinki and its later amendments. All patients gave written informed consent prior to their enrollment in the study.

SUSPECT was a non-interventional, cross-sectional study that took place between February 2011 and June 2013. No formal sample size calculation was performed. The planned number of patients (160) was defined on the basis of the recruiting capacity of the participating investigators. Data were collected during one routine visit to a non-rheumatologist investigator (orthopedists, PMR physicians, and ophthalmologists) practicing in university hospitals, regional hospitals, or in private practice. Patients aged 18–45 years at inclusion, with chronic back pain (>3 months) and back pain at night were eligible. Patients with diagnosed AS or SpA were excluded. The patients were evaluated for the presence of IBP based on the ASAS criteria [12] and SpA features according to the ASAS criteria for axial SpA [14]. Investigators were requested to refer any patient who presented with at least four of the five IBP symptoms and at least one additional SpA feature to a rheumatologist.

Demographic and baseline characteristics (duration of pain, presence of IBP symptoms, and SpA features) were collected during a single routine visit on a first case report form (CRF). For referred patients, investigators completed a second CRF based on the information provided by the rheumatologist (confirmation of diagnosis, diagnosis parameter, treatment initiated). Because this study was observational, HLA-B27 determination was not performed systematically (either by the investigator or the rheumatologist); however, the information was reported in the CRF when

HLA-B27 results were available. The proportion of patients with HLA-B27-positive results was therefore not calculated. The number of patients with a positive HLA-B27 result is given for information purposes only; these data should be considered with caution.

Outcome Measures

The proportion of patients with confirmed diagnosis of axial SpA was evaluated and the characteristics of the patients referred to a rheumatologist were summarized.

Statistical Analysis

Descriptive analyses were performed using the SAS package for Windows, version 9.2 (SAS, Cary, NC, USA) on the full analysis set, which consisted of all enrolled patients with available information. Five subpopulations were defined: patients referred to a rheumatologist, patients agreeing to visit a rheumatologist, patients for whom feedback from the rheumatologist was available, patients with confirmed SpA diagnosis and patients with confirmed diagnosis not meeting the referral criteria (see flow chart in Fig. 1 for more details).

RESULTS

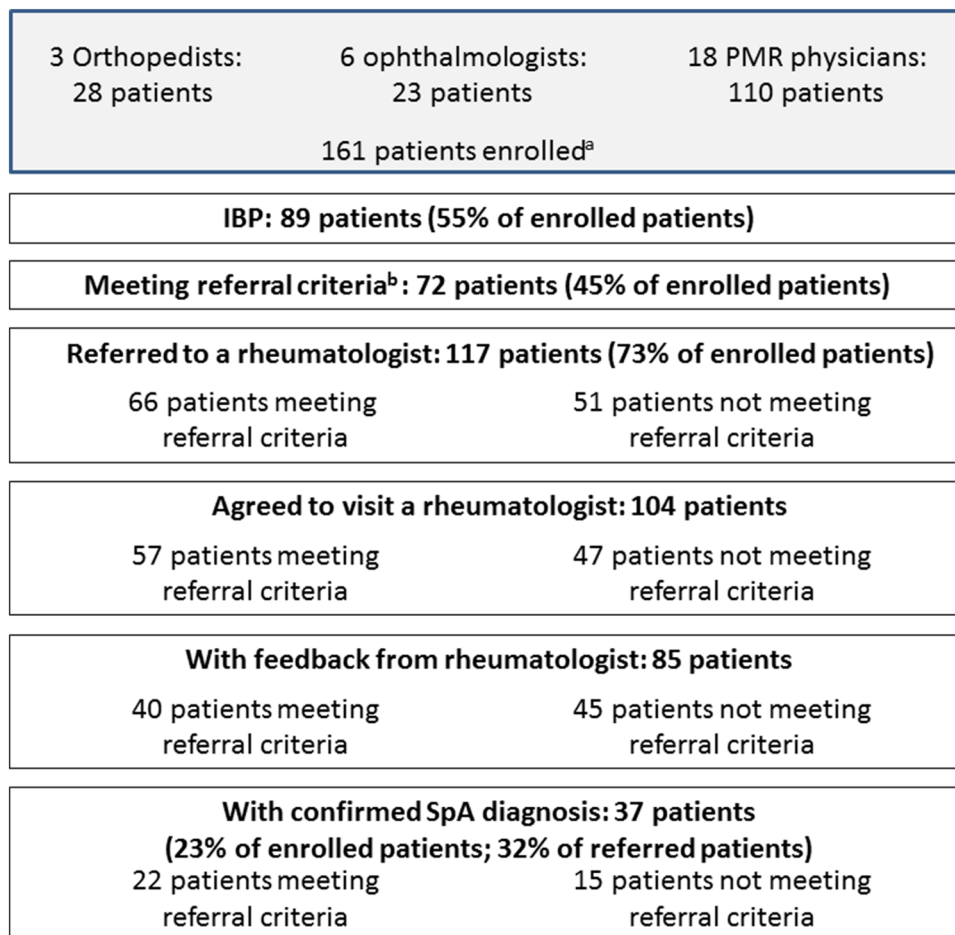
Patient Demographics

A total of 27 investigators (three orthopedists, six ophthalmologists, and 18 PMR physicians) recruited 161 patients meeting the eligibility criteria for the study (patients aged between 18 and 45 years old, with chronic back pain and pain at night, having signed an informed consent and without known axial SpA). Patients ranged in age from 20 to 53 years,

with an average age of 36 years [standard deviation (SD): 8 years]. Although the inclusion criteria stated an age limit of <45 years, 20 patients exceeded the age limit (eight patients had an age equal to 45 years). However, the decision was made to include these 20 patients in the full analysis set. Indeed, most of them (15/20) developed their back pain before 40 years of age and the others (5/20) had at least 2 SpA features. Of the 161 recruited patients, 46% were male.

Baseline Characteristics and Referral to a Rheumatologist

Of the 161 enrolled patients with back pain, 89 patients (55%) were diagnosed with IBP (at least four of five symptoms of IBP). The most frequently reported IBP symptoms (>85%) were age at onset younger than 40 years and pain at night (Table 1). The mean duration of back pain at the time of inclusion was 4.2 years (SD: 5.4 years; range, 2.5 months–25 years). A total of 130 patients (81%) presented at least one additional SpA feature. The most frequently reported additional SpA feature (collected before referral) was good response to NSAIDs (42%). A total of 72 patients met the referral criteria and 66 of them were referred to a rheumatologist. Although they did not meet referral criteria, 51 additional patients were referred to a rheumatologist. From these 51 patients, 46 fitted less of five IBP criteria and five had no SpA features according to the referring physician. Then, a total of 117 patients were advised to consult a rheumatologist, 104 agreed to do so and feedback was collected on 85 patients (Fig. 1). A diagnosis of SpA was confirmed for 37 patients (23.0% of the 161 enrolled patients, 31.6% of the referred patients, and 43.5% of the 85 patients with a

Fig. 1 Patient disposition flow chart

IBP: inflammatory back pain; SpA: Spondyloarthritis; PMR: Physical medicine and rehabilitation

^a Full analysis set

^b 4 out of 5 IBP symptoms and at least one additional SpA feature

rheumatologist feedback), 15 of which had not met the referral criteria.

Characteristics of Patients with Confirmed Axial SpA Diagnosis

In general, rheumatologists felt confident with their diagnosis (mean score >7 on a 0–10 scale). The main characteristics of patients with confirmed diagnosis of axial SpA are presented in Table 2. The mean age (34, SD: 8 years), sex ratio (41% male), and mean back pain duration (4.2, SD: 5.4 years) of patients with confirmed diagnosis of axial SpA are similar to those of the

total study population. All patients meeting referral criteria had at least four IBP symptoms as specified in the protocol. Some discrepancies were observed between the SpA features recorded by the investigator and those recorded by the rheumatologist. For example, sacroiliitis on imaging (X-ray, MRI, or CT scan) was the most frequent SpA feature reported by the rheumatologist (57%, Table 2), whereas good response to NSAIDs for back pain was the most frequent SpA feature reported by investigators (42%, see previous paragraph).

Based on data from the rheumatologist evaluation, 33 of the 37 patients with

Table 1 IBP symptoms

Patients	All enrolled <i>N</i> = 161	All referred <i>N</i> = 117	With feed-back from rheumatologist <i>N</i> = 85	With confirmed diagnosis <i>N</i> = 37	With confirmed diagnosis but not meeting referral criteria <i>N</i> = 15
Number of IBP symptoms, <i>n</i> (%)					
4 and 5	89 (55.3)	71 (60.7)	44 (51.8)	23 (62.1)	1 (6.7)
IBP symptoms, <i>n</i> (%)					
Age at onset <40 years	144 (89.4)	104 (88.9)	71 (83.5)	33 (89.2)	11 (73.3)
Insidious onset	106 (65.8)	78 (66.7)	52 (61.2)	23 (62.2)	5 (33.3)
Improvement with exercise	92 (57.1)	71 (60.7)	48 (56.5)	24 (64.9)	5 (33.3)
No improvement with rest	85 (52.8)	69 (59.0)	42 (49.4)	20 (54.1)	5 (33.3)
Pain at night (improvement by getting up)	141 (87.6)	101 (86.3)	72 (84.7)	34 (91.9)	12 (80.0)

IBP inflammatory back pain, *n* number of patients in the specified category

confirmed diagnosis of SpA fulfilled the ASAS classification criteria for axial SpA (89%). The imaging arm criteria (sacroiliitis on imaging and at least one SpA feature) were met by 22 patients, whereas the clinical arm criteria (positive HLA-B27 result and at least two SpA features) were met by 11 patients.

Overall, a new diagnosis of axial SpA was confirmed by the rheumatologist for about one-third of the referred patients.

DISCUSSION

In the SUSPECT study, 117 patients were referred to a rheumatologist (73% of the 161 enrolled patients) and diagnosis was confirmed for 37 patients, i.e., 23% of the enrolled patients and 32% of the referred patients. This proportion is similar to the prevalence observed in the literature [2, 8, 20, 22–27]. The

primary healthcare professionals involved in the SUSPECT study were not general practitioners, but mainly PMR physicians and, to a lesser extent, orthopedists and ophthalmologists. Recently it was suggested that increasing awareness of SpA in primary healthcare professionals should not only focus on general practitioners but also target physicians who might encounter patients with potential extra-articular manifestations such as inflammatory bowel disease, psoriasis, or uveitis in their daily practices [28]. Our study shows that this is a valid point, underscoring the role of PMR physicians, orthopedists, and ophthalmologists in early diagnosis of SpA.

The fact that about 40% (15/37) of the patients with confirmed diagnosis did not meet the referral criteria proposed in the SUSPECT protocol suggests that these criteria (four of five IBP criteria and one additional SpA

Table 2 Characteristics of patients with confirmed axial SpA diagnosis

Patients	With confirmed diagnosis <i>N</i> = 37	With confirmed diagnosis and meeting referral criteria <i>N</i> = 22	With confirmed diagnosis but not meeting referral criteria <i>N</i> = 15
Demography			
Male, <i>n</i> (%)	15 (40.5)	8 (36.4)	7 (46.7)
Mean age (SD)	34.0 (7.7) years	34.4 (7.1) years	33.4 (8.7) years
Mean back pain duration (SD)	50.8 (65.3) months	50.1 (64.7) months	52.0 (68.9) months
Number of IBP symptoms, <i>n</i> (%)			
4 and 5	23 (62.1)	22 (100)	1 (6.7)
IBP symptoms, <i>n</i> (%)			
Age at onset (<40 years)	33 (89.2)	22 (100)	11 (73.3)
Insidious onset	23 (62.2)	18 (81.2)	5 (33.3)
Improvement with exercise	24 (64.9)	19 (86.4)	5 (33.3)
No improvement with rest	20 (54.1)	15 (68.2)	5 (33.3)
Pain at night (with improvement upon getting up)	34 (91.9)	22 (100)	12 (80.0)
Additional SpA features, <i>n</i> (%) as reported by the rheumatologist			
Arthritis	4 (10.8)	1 (4.5)	3 (20.0)
Enthesitis of the heel	4 (10.8)	2 (9.1)	2 (13.3)
Uveitis confirmed by ophthalmologist	7 (18.9)	5 (22.7)	2 (13.3)
Dactylitis	1 (2.7)	1 (4.5)	0 (0.0)
Psoriasis	3 (8.1)	1 (4.5)	2 (13.3)
Inflammatory bowel disease (Crohn, UC)	0 (0.0)	0 (0.0)	0 (0.0)
Family history of axial spondyloarthritis, Crohn, psoriasis	7 (18.9)	2 (9.1)	5 (33.3)
HLA-B27 positive ^a	22	13	9
Elevated CRP or ESR	5 (13.5)	3 (13.6)	2 (13.3)
Good response to NSAIDs for back pain	6 (16.2)	4 (18.2)	2 (13.3)

Table 2 continued

Patients	With confirmed diagnosis <i>N</i> = 37	With confirmed diagnosis and meeting referral criteria <i>N</i> = 22	With confirmed diagnosis but not meeting referral criteria <i>N</i> = 15
Sacroiliitis on imaging (X-ray, MRI, or CT scan)	21 (56.8)	11 (50.0)	10 (66.7)

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *HLA* human leukocyte antigen, *IBP* inflammatory back pain, *n* number of patients in the specified category, *NSAID* nonsteroidal anti-inflammatory drug, *SD* standard deviation, *SpA* axial spondyloarthritis

^a HLA-B27 was not systematically requested by the investigator or rheumatologist but was only collected in the CRF when results were available. Therefore the proportion of patients with positive HLA-B27 results is not presented (total number of patients tested for HLA-B27 and number of patients with negative HLA-B27 results is unknown)

feature) may be too stringent. Several studies have questioned the use of IBP as the main clinical feature in the diagnosis of axial SpA [11, 24] due to the specificity of IBP with regards to its low prevalence among chronic back pain patients [6]. Shortly after the end of the study ASAS published recommendations for the early referral of patients with suspicion of axial SpA [29]: chronic back pain with onset before 45 years of age was retained as entry criterion; and IBP, along with other axial SpA characteristics (HLA-B27 positive, sacroiliitis on imaging, peripheral and/or extra-articular manifestation, positive family history for SpA, good response to NSAIDs and elevated acute phase reactants) was named as one of the additional parameters, which should lead to referral in those patients. This was defined in line with the ASAS classification criteria in which IBP was not proposed as a mandatory entry criterion but as a SpA feature. IBP is, and should remain, a key characteristic for screening patients in primary care settings; however, primary healthcare professionals should keep in mind that absence of IBP should not exclude a diagnosis of SpA [30]. This seems to be the case in the current study, where two-thirds of the patients with confirmed diagnosis that did not meet the referral criteria (10/15) did not meet

the IBP criteria (presence of only three of the IBP symptoms). Overall, all the referred patients would have met the referral criteria as proposed by the recently published ASAS recommendation [29].

When the ASAS classification criteria for axial SpA were applied, 89% of the patients with confirmed diagnosis (33/37 patients) were classified as having axial SpA: one-third via the clinical arm of the ASAS criteria, which shows the importance of this arm for early diagnosis of axial SpA. These results are more or less in line with the results observed in 2 cohort studies, the DESIR and the SPACE cohorts [31, 32], which reported that 40% and 50% of patients, respectively, met the clinical arm criteria.

This study had several limitations; therefore, the results should be interpreted with caution. They are, however, mostly supportive of the current literature and informative for any healthcare professional dealing with early diagnosis of SpA. Because of the non-interventional nature of the study, it was not mandatory for the orthopedist, PMR physician or ophthalmologist to refer all patients included in the study to a rheumatologist. This might have led to a selection bias in the estimation of axial SpA in patients with chronic back pain. The fact that

not all patients referred to a rheumatologist satisfied the referral criteria as stipulated in the protocol (44%) introduces another bias that may have complicated the interpretation of the sensitivity and specificity of the referral criteria used. This fact, combined with the limited number of patients included in the study, led to the decision to not compute the sensitivity and specificity of the referral criteria. Another limitation was that feedback from the rheumatologist was only received from 85 patients out of the 117 patients who were referred. It could be suggested that the rheumatologists provided feedback more readily in the case of a patient diagnosed with SpA, which may have led to another bias in the estimation of the prevalence of SpA.

CONCLUSIONS

The high percentage of axial SpA in patients with chronic back pain visiting PMR physicians, orthopedists, and ophthalmologists in this study suggests that these healthcare professionals may play a key role in shortening the delay between the first symptoms and the formal diagnosis of axial SpA. The fact that approximately 40% of the patients with a confirmed diagnosis did not meet the referral criteria of the study (four of five IBP criteria and one additional SpA feature) suggests that these criteria may be too stringent. When the ASAS classification criteria for axial SpA were applied, 89% of the diagnosed patients were classified as having axial SpA, with approximately one-third of patients diagnosed according to the clinical arm of the ASAS criteria.

Early diagnosis of SpA in patients with chronic back pain could be improved by appropriate education and information on

axial SpA for non-rheumatologists. Overall, the recent developments that allow earlier diagnosis, namely, the detection of inflammation signs with MRI, the set-up of referral strategies (of which the SUSPECT study is a part), as well as the development of new drug therapies may make a positive difference in the diagnosis and early management of patients with axial SpA.

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Compliance with Ethics Guidelines. The SUSPECT study was approved by the ethics committee of Erasme Hospital (Brussels, Belgium) and conducted according to local regulations. It has therefore been performed in accordance with the ethical standard laid down in the 1964 declaration of Helsinki and its later amendments. All patients gave written informed consent prior to their enrollment in the study.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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