Clinical significance of inflammatory back pain for diagnosis and screening of patients with axial spondyloarthritis

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ABSTRACT

Inflammatory back pain (IBP) is the leading symptom of patients with spondyloarthritis (SpA), but its value for diagnosis, classification and screening in primary care is not well defined. Although often used since 1977, its clinical significance has not been extensively studied. As shown recently, most but clearly not all patients with axial SpA have IBP. Therefore IBP has not been included in current criteria for axial SpA as a first-line criterion. The value of IBP for diagnosis of SpA increases in the presence of other more or less sensitive and specific features of SpA such as response to exercise and physical therapy and/or treatment with non-steroidal anti-inflammatory agents.

INTRODUCTION

Inflammatory back pain (IBP) is the leading symptom of patients with spondyloarthritis (SpA),[1] but its value for diagnosis, classification and screening in primary care is not well defined. IBP was first mentioned and described as a specific clinical feature of ankylosing spondylitis (AS), the prototype of SpA, by Calin *et al*[2] in 1977 (box 1). The well-known problem of a significant delay in diagnosing AS[3] has led to a series of proposals for classification criteria for IBP over the last few decades. IBP has long been a central criterion of classification published for AS[4 5] and SpA.[6 7] In the absence of direct diagnostic criteria, such symptoms have often also been used for diagnosis.[8] However, the definitions of IBP used in these criteria sets are variable, and views on the clinical usefulness, sensitivity and specificity of this item, and its value for classification and diagnosis, are evolving. New definitions of IBP[9 10] have been proposed (boxes 2 and 3), but chronic back pain rather than IBP has become the first-line criterion in the new Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axial SpA.[11]

The fact that, in a recent survey of general practitioners (GPs), inconsistencies in perceptions and approaches to the diagnosis and management of AS were identified[12] has confirmed that there are problems in understanding the concept and definitions of SpA. As concluded by the authors of that paper, education in primary care may improve early detection and hence outcome of axial SpA (includes AS).

This article describes and discusses the current situation in order to enhance the understanding of rheumatologists of the clinical and scientific significance of the term IBP, especially in relation to the new terminology, axial SpA. To this end, we review the conceptual value of IBP as a tool for diagnosis, classification and screening of patients with back pain and SpA. In box 4, an overview of the different domains of IBP that are possibly relevant is given.

However, we stress that the whole differential diagnosis of back pain—for example, infection, infarction, malignancy—is beyond the scope of this review.

PREVALENCE OF IBP AND SPA

As a major symptom of SpA, IBP is not only important to rheumatologists, because back pain is such a common symptom in patients presenting in the offices of GPs and orthopaedic surgeons.[13] In British GP surgeries, the prevalence of IBP related to SpA has been found to be ~5%.[14] The prevalence in chiropractic settings has been shown to be comparable.[15] The prevalence of SpA in rheumatologists' offices may actually be significantly higher, which may reflect the pretest probability of the entity. The overall prevalence of SpA has been estimated to be ~1%, similar to that of rheumatoid arthritis (for a review, see Akkoc *et al*[16]).

AXIAL AND PERIPHERAL SPA

SpA are a heterogeneous group of rheumatic diseases, which have been recently divided into two subgroups according to the predominant symptoms,[11 17] which can be localised to either the spine (axial SpA) or the peripheral joints (peripheral SpA). Other common differentiations used to diagnose or classify patients are disease-defining features: spinal stiffness (the cardinal symptom of AS); psoriasis; inflammatory bowel disease (Crohn's disease or ulcerative colitis); history of a triggering infection in the enteral or urogenital tract (reactive arthritis). In the absence of any of these features, the term undifferentiated SpA (uSpA) is often used.[18–20]

Box 1 Inflammatory back pain according to historical data[2]

- Age <40 years
- Persisting ≥3 months
- Morning stiffness
- Insidious onset
- Improvement with exercise

If at least four of the five criteria are fulfilled, sensitivity is 95% and specificity is 85%.

Box 2 Inflammatory back pain according to study data[9]

These criteria have been developed in patients with:
- Age at onset of back pain <45 years
- Time period of the onset of back pain 3 months

In this group, the following combination of four items was most relevant:
- Morning stiffness of >30 min duration
- No improvement in back pain with rest
- Awakening because of back pain during the second half of the night
- Alternating buttock pain

If at least two of the four criteria are fulfilled, sensitivity is 70% and specificity is 81% (positive likelihood ratio 3.7).
If at least three of the four criteria are fulfilled, sensitivity is 33% and specificity is 98% (positive likelihood ratio 12.4).

Box 3 Inflammatory back pain according to expert opinion[10]

- Improvement with exercise (OR 23.1)
- Pain at night (OR 20.4)
- Insidious onset (OR 12.7)
- Age at onset ≤ 40 years (OR 9.9)
- No improvement with rest (OR 7.7)

If at least four of the five criteria are fulfilled, sensitivity is 77% and 80%, specificity is 92% and 72%, in the patients participating in the workshop and the validation cohort, respectively.

Box 4 Possibly relevant domains of inflammatory back pain

- Age of patient
- Duration of symptoms
- Location
  - Lower back
  - Alternating buttock pain
- Signs of inflammation
  - Morning stiffness
  - Night pain
- Mode of onset
  - Insidious
- Improvement
  - By exercise
  - Not with rest
  - Non-steroidal anti-inflammatory agents

Box 5 Key research recommendations

- Evaluate the performance of items relevant for a classification of inflammatory back pain in primary care
- Analyse the performance of items indicating a response to therapy
- Study the combination of clinical items with human leucocyte antigen B27
- Examine the relevance of morning stiffness related to its duration
- Establish a common screening tool for axial spondyloarthritis

A major problem with the use of differentiation into axial and peripheral disease as part of the classification system is that there is substantial overlap between the two. In recently published data from the Spanish registry, back pain was reported as the first symptom in 72% of AS patients and 56% of uSpA patients, whereas lower limb arthritis occurred first in 35% of uSpA patients and 20% of AS patients.[21] Furthermore, the coexistence of both axial and peripheral symptoms occurs often—for example, 25% of the patients in the Spanish registry.[22] A recent analysis of a large group of patients with peripheral SpA revealed that more than 80% were classified as undifferentiated.[20] Preliminary results from a cross-sectional German study in a primary care setting showed that fewer patients with axial SpA had established AS than the subset diagnosed as having non-radiographic axial SpA because of the lack of structural changes in the sacroiliac joints.[23]

These SpA subsets have recently been compared in the German registry, GESPIC.[24] The clinical results suggested a similar degree of clinical symptoms, including IBP. This finding is an important argument for early axial SpA and the more advanced AS being considered as one disease. The complexity arises because not all patients with axial SpA will develop structural changes in the axial skeleton.[25]

SENSITIVITY AND SPECIFICITY OF IBP CRITERIA

The sensitivity and specificity of IBP (for the classification of axial SpA or AS) is critically related to the pretest probability of the patient having the disease[11 26] and to the stringency of the IBP criteria used.[27] When the prevalence of SpA in the office of a rheumatologist is high (25–50%), the performance is much better than in a GP setting (5% and less). When stringent criteria were used, the likelihood ratio of having SpA in the presence of three out of four IBP criteria was found to be >12.[9 28]

The sensitivity of IBP for a diagnosis of axial SpA has been shown to be ~70%.[9] That is the main reason why IBP has recently been removed as an entry criterion for classification of axial SpA.[17] The performance of chronic back pain as an entry criterion is, although less specific than IBP, superior, and it increases the sensitivity of criteria for axial SpA.

The performance of the first IBP criteria on a population basis already indicated its limited use as a screening tool: of 1880 people who reported back pain when answering a questionnaire, almost 20% fulfilled IBP criteria, but only 16 had AS.[29] In another population-based study, >60% of patients (n=90) had symptoms suggestive of IBP,[30] but only some of them had MRI-proven sacroiliitis, 47% in the human leucocyte antigen B27 (HLA-B27+) group and 4% in the B27– group. In another study in which only patients with IBP (n=170) were included, >60% had a diagnosis of SpA.[31] There have been several studies in which only patients with IBP were included.[32–34] However, this precludes further analyses of the mode of back pain in axial SpA.

Therefore, current cohort studies have mainly included young patients with chronic back pain rather than focusing only on IBP.

In studies on the classification criteria,[17] the IBP expert[10] and the Berlin[9] criteria for IBP performed similarly well as candidate criteria, and both were superior to the Calin criteria[2] in terms of specificity.

DEFINITIONS OF IBP

The different definitions of IBP published to date are shown in boxes 1–3, and an overview of all possible items and domains is given in box 4. The main items are the same: (1) a relatively young age at onset (<40 or <45 years); (2) morning stiffness as a major symptom associated with inflammation, which may be due to the diurnal variation in the release of cytokines such as interleukin 6[35]; (3) chronicity of back pain, which implies a time period defined as lasting for more than 3 months[36–38]; and (4) improvement generated by movement rather than by rest. In addition, the mode of onset (insidious rather than rapid) has been put forward, but that did not come out in all studies.[9] The localisation of pain has usually been assigned to the lower back.

DOMAINS AND ITEMS OF IBP

Duration of symptoms

The following general time frames are given for the duration of back pain on the basis of resolution of symptoms: acute low back pain lasts less than 6 weeks, subacute low back pain lasts between 6 and 12 weeks, and chronic low back pain persists for more than 12 weeks.[39] In a recent Dutch study, 35% and 10% of the patients with low back pain still had back pain after 12 and 52 weeks, respectively.[40] In a recent survey, almost 20% of the participants indicated that they had had back pain for more than 6 months.[41] However, the duration of back pain is an item that may be potentially selective in terms of chronicity. Indeed, its value has been considered so important for the definition of IBP that, in one criteria set, a duration of 3 months of pain is a prerequisite.[9]

Furthermore, the definition of disease duration for AS refers to the time point when IBP first occurred.[42] However, the exact duration of back pain or IBP in SpA has not been studied, but the cut-off for chronic back pain has been set at 3 months by analogy. This has also influenced management recommendations.[43,44] What has not been defined or discussed is whether the 3 months of back pain need to have occurred consecutively. As it has recently been shown that the pattern of flares on top of a constant level of back pain is the most common course in AS, it could well be that there is some variance.[45] Intermittent pain was also reported by more than half of the patients reporting pain in the survey.[41]

The duration of morning stiffness has been recently studied[9] and found to best discriminate IBP from non-specific or mechanical forms at 30 min. This implies that a shorter duration of morning stiffness is less specific, whereas a longer duration is more suggestive of inflammatory disease.

Age at onset

Another important clinical feature is the age of the patient, which, for IBP, has been usually set at <40 or <45 years. This is not data-based, but appears reasonable since the mean age of onset of AS is 26 years.[13] As the peak prevalence of low back pain in the population is between 45 and 60 years,[13 38] this item is also of potential use in terms of selection. Indeed, age has been considered so important for the definition of IBP that, in one criteria set, age <45 years is a prerequisite.[9]

This choice of cut-off for IBP indicates that the definition is mainly aimed at identifying patients with early disease, although it is clear that IBP may still be present in much older patients with longstanding disease, which underlies the rationale for anti-(tumour necrosis factor) agents being used even in patients with advanced disease and total spinal ankylosis.[46] However, it needs to be stressed that it has not yet been addressed whether the way IBP presents is different in young patients with early disease and older patients with longstanding disease. Of note, the demographic from two recent clinical trials with axial SpA patients not fulfilling the New York criteria revealed that there are two possible subsets: one with a mean age of 28 years and a symptom duration < 3 years,[47] and another with a mean age of 38 years who had symptoms <5 years.[48]

Location and cause of pain

The anatomical location of IBP as an early sign of axial SpA has not been systematically studied to date. Recent registry data indicate that patients with early SpA most often report pain in the lower back.[22] Thus axial SpA is a differential diagnosis for non-specific low back pain[49] and other common causes of mechanical back pain, such as degenerative disc disease, which are now often detected by MRI techniques.[50] Indeed, the so-called Modic lesions seen in degenerative disc disease are most commonly found at the level of L4/L5 and L5/S1.[51]

Alternating buttock pain was first proposed as an important item for classification of SpA in 1991,[6] when it was separated from other criteria for IBP, which had not been specifically evaluated in that study. In a comparative study, alternating buttock pain proved to be more specific than sensitive.[9] Indeed, it has not been reported in patients with low back pain to date.

Mode of onset

The mode of onset of back pain has been identified as a tool to differentiate patients with sciatic pain, who are much more likely to have sudden onset.[52] In contrast, insidious onset of back pain is reported by 50–60% of patients with IBP due to SpA.[53] However, this rather serves as a differentiating feature between acute and chronic disease. In contrast with the recent expert study,[10] insidious onset did not differentiate between the AS and the control group in the largest study to date of patients with chronic back pain.[9]

Sleep disturbance due to pain

Awakening in the second half of the night was first reported to be indicative of AS by Gran *et al* in 1985.[54] This was clearly confirmed in a comparative study, where this item was not very sensitive but rather specific.[9] On the other hand, there is a strong association between sleep disorders and back pain.[55] This may make the interpretation of this symptom difficult. However, sleep disorders are unlikely to improve when anti-inflammatory treatment is administered (see below).

The items 'waking up in the second half of the night' and 'alternating buttock pain' work best in combination with other items that are more sensitive but less specific.

RESPONSE TO THERAPY

An item of major importance for diagnosis and classification of IBP and SpA has become the response to therapy,[9–11 17] which is unusual as diagnosis and therapy are normally considered as separate domains. One reason for this development is that the

item 'improvement by movement' has always been one of the IBP criteria,[2] and this non-pharmaceutical intervention—which has also just been termed 'exercise'—has never been very precisely described, although physiotherapeutic interventions are an established tool in the care of patients with AS.[56] However, it is of interest that patients with acute low back pain are also advised to stay active rather than rest in bed, as there is little or no difference between the effect of bed rest and exercises or physiotherapy.[57]

The diagnostic utility of pharmaceutical interventions with non-steroidal anti-inflammatory agents (NSAIDs) was first described by Amor 20 years ago.[58] Accordingly, a good response to NSAIDs within 48 h is also one of the diagnostic criteria proposed by this author.[7 8] What has remained unclear since then is (1) whether the response to NSAIDs is already present and detectable after 24 h or less, (2) what dose of NSAIDs should be used, and (3) to what degree should the back pain actually improve. At the moment it is a rather subjective improvement in the patient's global assessment of pain.

A recent Cochrane review identified 65 trials on the efficacy of NSAIDs for short-term symptomatic relief in patients with acute and chronic low back pain without sciatica. The evidence for a marginal effect, but small effect sizes, in patients with non-specific low back pain rather confirms the preferential response in SpA.[59]

ADDITIONAL LABORATORY TESTS

What do we know about the performance of additional diagnostic tests such as laboratory tests (C-reactive protein (CRP), HLA-B27) and imaging (conventional radiography, MRI)? Rudwaleit *et al* [26,27] have developed an algorithm for the diagnosis of axial SpA on the basis of historical data. HLA-B27 and both imaging methods were identified as the strongest contributors to an increase in the likelihood of a diagnosis of SpA, whereas a raised serum concentration of CRP was only a weak contributor. The conclusion in the validation study for the new classification criteria for axial SpA was similar.[17]

ADDITIONAL IMAGING PROCEDURES

The usefulness of MRI, in addition to conventional radiography, has been demonstrated for diagnostic[33] and prognostic[60] purposes. Criteria for the definition have been published,[61] and examples have been extensively provided.[62]

SCREENING FOR AXIAL SPA

The final point of discussion in this review is the fundamental difference between diagnosis, classification and screening. In the algorithm, fulfilling IBP criteria increased the likelihood of a diagnosis of axial SpA threefold. Thus, starting from a probability of 5% in a patient with chronic back pain (see above), the likelihood ratio product is no higher than 20 when IBP criteria are fulfilled. Taken together, the performance of IBP criteria is completely different in a GP's office from a rheumatologist's office, because, in the latter, the pretest probability may be a lot higher than 5%.

However, the first referral recommendations proposed the use of IBP features and HLA-B27 testing for screening purposes at the level of the primary care physician,[63] but the performance of IBP criteria in that setting had not been studied in detail at that point. The first study to address this was performed in Berlin with orthopaedists and primary care doctors, who were requested to refer patients with chronic low back pain (duration >3 months; onset before 45 years of age) to a specialist rheumatology outpatient clinic if at least one of the following screening criteria was present[1]: IBP features,[2] positive HLA-B27[3] and sacroiliitis detected by imaging.[64] The fact that a diagnosis of axial SpA was made in 45% of all referred patients suggested that this constituted a very effective screening mechanism. A diagnosis of axial SpA was made in 34% if only one referral criterion was positive, and in 63% if there was more than one positive referral criterion. To learn more about the performance of IBP criteria in this setting, a randomised study in primary or secondary care settings is needed.

CONCLUSIONS

IBP is a major symptom of SpA, and knowledge about its clinical features has significantly increased over the last few decades. IBP criteria have been developed which have proven useful, especially in rheumatologists' offices, but probably less so in a GP setting. Thus, for screening purposes and early diagnosis, chronic back pain in relatively young patients is superior, and HLA-B27, x-rays and MRI of the sacroiliac joints are the most helpful additional diagnostic procedures. To make a diagnosis of axial SpA, the item of IBP alone has limited value; it clearly needs to be combined with other items that have been identified as useful in the diagnosis of axial SpA. Some proposals for future research are listed in box 5.

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Notes