

Quality of care, referral, and early diagnosis of axial spondyloarthritis

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Axial spondyloarthritis (axSpA) is a frequent chronic inflammatory rheumatic disease that affects mainly the axial skeleton, while patients with predominantly peripheral SpA suffer mainly from arthritis, enthesitis, and dactylitis [1]. The concept of spondyloarthritis also covers psoriasis, inflammatory bowel disease, and anterior uveitis which are also referred to as extramusculoskeletal manifestations [1]. The pathognomonic musculoskeletal findings of patients with axSpA are inflammatory, osteodestructive, and osteoproliferative changes in the sacroiliac joints (SIJ) and in spinal structures, many of which are of enthesal nature [1]. The most severe outcome is total spinal ankylosis which radiographically presents as “bamboo spine”; this has long been recognized as the clinically leading sign that led to the term ankylosing spondylitis (AS) [2, 3] which is now, based on the Assessment of SpondyloArthritis international Society (ASAS) classification criteria [4], slowly being replaced by the term radiographic axSpA (r-axSpA) that is largely equivalent to AS [5]. The diagnosis axSpA covers different stages, variable courses, and outcomes of one disease. For classification purposes, non-r-axSpA (nr-axSpA) is differentiated from r-axSpA because of differences in the approval status of biologic disease-modifying antirheumatic drugs (bDMARDs) [6], e.g., infliximab is not approved for nr-axSpA.

The treatment with bDMARDs has made quite a difference for patients with axSpA in the last decades, including the reduction of inflammation [7, 8] and the partial inhibition of new bone formation [8–10]. However, physical function and activity are also of major importance for patients with axSpA [11].

Diagnostic delay in patients with axSpA has been a well-known problem already for some time [12], for which various circumstances are responsible. The average delay in diagnosis in Germany is currently 5–6 years—slightly better than 20 years ago [13, 14]. The recent publication of international and national quality standards [15, 16] and management recommendations [17–19] has redirected the public interest to this aspect of health care in rheumatology. The first reason for the diagnostic delay is that back pain is simply very common and the associated clinical problems are usually over after about 6 weeks [20, 21]. The most common diagnosis in primary and secondary care for patients with chronic back pain is non-specific low back pain (LBP) [20, 21]. For these reasons, among others, guidelines initially advise against performing imaging diagnostics—unless there are warning signs for a specific cause of the LBP [22]. Nevertheless, LBP is the fourth most common cause of disability-adjusted life-years (DALYs) in people aged 25–49 [23]. One DALY corresponds to the calculated loss of one year of full health.

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Another problem is the time and personnel capacity of rheumatologists. This is linked to the question of how many patients with back pain need to be seen to make a diagnosis of axSpA. At the moment, the estimated pre-test probability of a diagnosis of axSpA in specialized tertiary centers is 20–40% [6]. Importantly, nonsteroidal anti-inflammatory drugs (NSAIDs) often work quite well initially in patients with axSpA, i.e. the pain is effectively relieved [24]. Incidentally, this contrasts with non-specific back pain [25].

The diagnosis of axSpA should be made on the basis of history, clinical examination, laboratory findings, imaging, and consideration of differential diagnoses [26–28]. Overall, it is important that not a single symptom is indicative of the diagnosis of axSpA, this makes a simple pre-selection of patients difficult. In accordance with the recently updated international recommendations [17] of ASAS and European League Against Rheumatism (EULAR), the aim of the German S3 guideline update [19], was also to provide evidence-based, practicable recommendations for early detection and diagnosis, including appropriate referral strategies for primary care, aiming for a further reduction in diagnostic delays. Furthermore, recent international and national quality standards recognize referral as an important feature of care for patients with axSpA [15, 16].

The goal of an early diagnosis of patients with axSpA is the timely initiation of adequate therapy and the avoidance of unnecessary further diagnostic procedures [15–19]. In addition, it is always a fundamental goal to reduce structural damage, especially new bone formation, mainly in order to prevent functional deficits [11] from occurring. However, the development of structural damage is rather variable in patients with axSpA [1, 3, 8, 9]. In a cohort of patients with inflammatory back pain (IBP) for less than 2 years, 20% of patients already had structural changes in the SIJ, while other patients never develop such spinal changes [29]. The famous bamboo spine occurred in no more than 20% of patients in the whole group of patients with axSpA [2, 8]. In addition, a larger proportion of patients with axSpA currently receive general medical or orthopaedic rather than specialist rheumatological care. Due to these various factors, making an early and correct diagnosis remains a challenge.

The central symptom in patients with axSpA is chronic back pain, i.e. this persists for longer than 3 months [30]. The prevalence of AS in patients with chronic back pain in general practices is about 5% [31]. A typical characteristic of axSpA is IBP [32], but its characteristics are not necessarily known by general practitioners (GPs). For example, only 5% of the 186 GPs surveyed in Norfolk County could name all the characteristics of IBP [33].

In about one-third of patients, it is not easy to decide whether IBP is present or not. In addition, there are different definitions of IBP [34–36]. IBP is therefore an important leading symptom, but its diagnostic value is limited [37–39]. Most recent data on the prevalence of IBP in the general population come from the National Health and Nutrition Examination Survey (NHANES) from 2009–2010 in which the prevalence was reported to be 5–6% [40].

Many studies testing referral strategies have been published [41–47]. The variables tested and the populations studied differ among studies. Clinical variables were tested alone or in combination with human leukocyte antigen (HLA)-B27 and/or diagnostic imaging. Clinical variables collected by simply interviewing patients have been most frequently studied. In all studies, it has been found that none of the variables tested is sufficient as a single parameter, as sensitivity and specificity are not sufficient to facilitate early detection. The collection of several variables, on the other hand, significantly increases the significance. However, the sole fulfilment of classification criteria can, of course, not ensure the diagnosis of axSpA. Sensitivity, specificity, and the likelihood ratio (LR) are of particular importance for the evaluation of individual variables. This indicates how many times a positive test result occurs more frequently in people with the disease compared to people without the disease. The pre-test probability is the estimated probability that a patient has a certain disease before additional information from diagnostic tests is added. The pre-test probability is derived from the prevalence of the disease, although the circumstances of the survey need to be further defined (e.g., care prevalence vs. population prevalence). Thus, population prevalence differs from the prevalence in a particular practice. Medical history data (e.g., risk factors) and findings from a previous examination such as magnetic resonance imaging (MRI) also play a role. The pre-test probability is thus also influenced by whether

the patient's presentation is in the primary or specialist setting. Post-test probability is the probability of disease after test results are available. Possible clinical variables in the diagnostic process include questions about the type of back pain, other symptoms of SpA, family history, and response to NSAID therapy. Some parameters such as very young age, female gender, and a previous visit to many physicians were found to be unfavourable in a recently published study [48].

If one summarises the results of all available studies, one has to say that the parameters for chronic back pain and age < 45 years are already quite good, as this alone usually achieves a frequency of axSpA of 30% and more in the patient population selected in this way. In many studies, HLA-B27 as a single parameter has the best performance. As shown in one of the last large studies, many combinations of clinical parameters work, with an LR of > 5 rarely being exceeded [47].

In this study, the sensitivity of a previously defined two-phase strategy was 87%, and the specificity was 56.8%, with positive and negative predictive values (PVs) of 24.8% and 96.4%, respectively. Several other combinations such as “good response to NSAIDs”, “morning stiffness > 30 min”, and “elevated C-reactive protein” performed best with a sensitivity of 91%, a specificity of 67%, and a positive PV of 31% and negative of 98%, respectively. On this basis, only three patients would need to be examined by a rheumatologist to establish the diagnosis of axSpA in one of them. This also shows a more or less consistent result in the studies: the negative PV is usually very good, while the positive value does not significantly exceed 30%—also a sign of the heterogeneity of the initial symptoms in axSpA patients [47].

The use of MRI [49] or polygenetic risk scores [50] in primary care is unlikely to solve the problem due to human and financial restrictions in the health care system. Nevertheless, MRI is likely to replace conventional radiography as the imaging modality of choice for the detection of sacroiliitis, and HLA-B27 will continue to play a role in diagnosis, classification, and also in most referral systems. Rheumatologists who are interested in an early diagnosis of axSpA should establish a simple system to identify as many early axSpA patients as possible—without having to see too many patients with other reasons for back pain—which can be a major challenge to the workload in everyday clinical practice.

Abbreviations

AS: ankylosing spondylitis

axSpA: axial spondyloarthritis

HLA: human leukocyte antigen

IBP: inflammatory back pain

LBP: low back pain

MRI: magnetic resonance imaging

NSAIDs: nonsteroidal anti-inflammatory drugs

r-axSpA: radiographic axial spondyloarthritis

Declarations

Author contributions

JB: Conceptualization, Formal analysis, Data curation, Writing—Original draft. UK and XB: Writing—Review & editing.

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