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REVIEW ARTICLE

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Delayed diagnosis of axial spondyloarthritis

ABSTRACT

Axial spondyloarthritis (axSpA) is an inflammatory joint disease whose predominant symptom is inflammatory pain in the spine. It occurs in approximately 1% of the population, with a higher incidence in men. Spinal pain in the course of spondyloarthritis is called inflammatory back pain. In addition to inflammatory back pain, other symptoms of axSpA include enthesitis, peripheral arthritis and extra-articular symptoms. A patient's family history and human leukocyte antigen B27 (HLA-B27) should also be considered, as these correlate closely with a higher incidence of spondyloarthritis. AxSpA is often underdiagnosed, and no specific serological test or physical examination can determine the diagnosis of spondyloarthritis. Despite good knowledge of the disease, the time between the first symptoms and diagnosis is still too long, which adversely affects the subsequent treatment options, as well as the mental and economic condition of patients. Patients are not referred to a rheumatologist quickly enough. Therefore, the features of inflammatory back pain, the symptoms associated with axial spondyloarthritis and the diagnostic tests should be well known by general practitioners and other specialists to whom patients with pain are first referred. This would accelerate accurate diagnosis and prompt implementation of appropriate treatment. This paper discusses symptoms of axSpA and emphasises the importance of prompt diagnosis in patients with complaints typical of spondyloarthritis.

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KEY WORDS: ankylosing spondylitis; axial spondyloarthritis; delayed axial spondyloarthritis

INTRODUCTION

Axial spondyloarthropathies (axSpA) are a group of inflammatory rheumatic diseases involving the axial skeleton and sacroiliac joints [1]. The prevalence of axSpA worldwide varies between 0.5 and 1.5%, and the ratio of affected men to women is 3:1 [2, 3]. The first symptoms appear before the age of 45, peaking in patients aged 20–30 [4]. In addition to axial symptoms, peripheral arthritis and enthesitis are sometimes present, as are numerous extra-articular manifestations, including uveitis, psoriasis or nonspecific inflammatory bowel diseases [5, 6].

A frequently assessed parameter for diagnosing, evaluating the activity and controlling the disease is C-reactive protein (CRP), usually elevated in axSpa patients [7]. The presence of human leukocyte antigen B27 (HLA-B27) is also important for diagnosis and is found in approximately 90% of patients [8, 9]. It should be remembered that the incidence of HLA-B27 in the general population is approximately 10%, making it a sensitive but not very specific marker of the disease [10].

DIAGNOSTIC CRITERIA FOR AXSPA

According to the 2010 Assessment of SpondyloArthritis International Society (ASAS) guidelines, axSpA is divided into radiographic axial spondyloarthritis (r-axSpA), in which inflammatory changes in the sacroiliac joints (sacroilitis) are present on radiographic (X-ray) examination, and non-radiographic axial spondyloarthritis (nr-axSpA), in which X-ray changes are absent. Inflammation is evident on magnetic resonance imaging (MRI) in the case of nr-axSpA. Due to the lack of clinical differences, r-axSpA includes ankylosing spondylitis (AS) [11, 12]. The common features of the 1984 modified New York criteria for AS and the ASAS criteria, which help diagnose axSpA, are chronic inflam-

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Table 1. The 1984 modified New York criteria for ankylosing spondylitis (AS) [13]

Clinical criteria
Lower back pain persisting for ≥ 3 months, improving with exercise but not with rest Limited range of motion in the lumbar spine in both sagittal and coronal planes Limited chest expansion, compared with the normal status matched to age and sex
Radiological criteria
Bilateral sacroiliitis grade 2–4 or unilateral sacroiliitis grade 3–4
Definitive diagnosis — radiological criterion and ≥ 1 clinical criteria met Probable diagnosis — 3 clinical criteria met or radiological criterion only

matory back pain and inflammatory changes on imaging studies [13] (Tab. 1–3).

CHARACTERISTICS OF INFLAMMATORY BACK PAIN

Inflammatory back pain lasts over three months, presents before the age of 45, resolves after exercise, and responds adequately to nonsteroidal anti-inflammatory drugs [14, 15]. Approximately 80% of people have experienced back pain in their lifetime [16]. Therefore, it is essential to distinguish inflammatory back pain from pain due to mechanical causes (Tab. 3), discopathy or internal organ pathologies [17]. It is important to understand that untreated axSpA leads to progressive spinal stiffness as a result of the formation of irreversible connections between the intervertebral joints, leaving patients disabled [18]. Treatment of the disease is most effective when inflammation predominates, while it is less effective when lesions are present [19].

Table 2. Diagnostic criteria for axial spondyloarthritis (axSpA) according to the 2010 Assessment of SpondyloArthritis International Society (ASAS) [13]

Criteria can be applied to patients with lower back pain persisting ≥ months and first occurring < the age of 45 and sacroiliitis documented by imaging (MR or X-ray) and ≥ 1 other feature of SpA or the presence of HLA-B27 and ≥ 2 other features of SpA:
Inflammatory back pain Peripheral arthritis Enthesitis (within the heel) Uveitis Dactylitis Another disease (psoriasis, Crohn's disease, ulcerative colitis) A positive response to nonsteroidal anti-inflammatory drugs A family history of spondyloarthritis The presence of HLA-B27 Elevated CRP levels after excluding other causes

MRI—magnetic resonance imaging; X-ray—radiological examination; HLA-B27—human leukocyte antigen B27; CRP—C-reactive protein

Table 3. Distinguishing features of inflammatory and mechanical back pain [13]

Feature	Inflammatory back pain	Mechanical back pain
Patient's age	Before the age of 45	At any age
Onset of pain	Insidious, escalating	Often acute
Duration of pain	Over 3 months	Varies
Pain during the night	Most severe in the second half of the night	Severity independent of day and night
Effect of physical activity on pain intensity	Reduction after physical activity	Exacerbation during physical activity, rest reduces pain
Morning stiffness in the spine	More than 30 minutes	Short-term
Response to nonsteroidal anti-inflammatory drugs	Good	Varies
Location of pain	Mainly lumbar spine in the gluteal region, does not radiate to lower limbs	Any part of spine, radiates to lower limbs
Nature of pain	Chronic, does not cause numbness, burning or tingling	Often acute, may cause tingling, numbness and burning

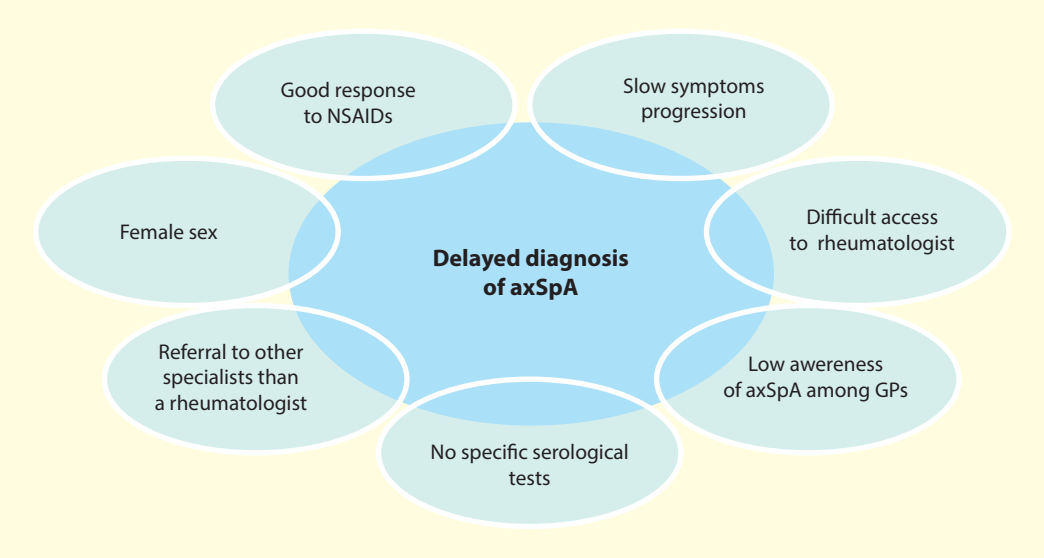

Figure 1. Factors delaying delaying axial spondyloarthritis (axSpA) diagnosis [28]. NSAIDs — nonsteroidal anti-inflammatory drugs. GP — general practitioner

FACTORS CONTRIBUTING TO DELAYED DIAGNOSIS OF AXIAL SPONDYLOARTHRITIS

Despite the increasing knowledge of axSpA, it still provides many diagnostic difficulties, and consequently, it remains undiagnosed until several years after the onset of symptoms. The average time from the first symptoms of axSpA to diagnosis is 11 years in Europe and 13 years in the United States [20]. The European Map of Axial Spondyloarthritis (EMAS) study conducted in 13 European countries reported the longest delays in Norway and Slovenia, while the shortest were found in the UK and Germany [21]. Due to the often atypical course and initially uncharacteristic symptoms, diagnosis in women is made later than in men [22]. Also, as axSpA is considered to be a predominantly male disease, women are often underdiagnosed. In women, the clinical manifestations are less characteristic; often, the predominant symptom is not inflammatory back pain but mainly cervical and thoracic spine complaints; sometimes, the pain may be generalised and also involve peripheral joints [23, 24]. It tends to be oligoarticular, affecting the sternoclavicular and temporomandibular joints [25]. It is worth mentioning that differences in the severity and nature of symptoms may be due to the effects of oestrogens. Oestrogens have an anti-inflammatory effect and also antagonise the action of tumour necrosis factor alpha (TNF-α). Unfortunately, partly due to this correlation, women show poorer effects of biological treatment of axSpA [26]. The EMAS study demonstrated that female sex is one of the main factors delaying axSpA diagnosis [21]. Women were most commonly misdiagnosed with fibromyalgia [27]. A US study found that most patients with lower back pain saw general practitioners, orthopaedic surgeons and chiropractors, while a small proportion saw rheumatologists (Fig. 1) [28].

It is estimated that most misdiagnoses and delayed diagnoses of axSpA were found among general practitioners and orthopaedic surgeons [29]. Symptomatic effects and the prescription of nonsteroidal anti-inflammatory drugs (NSAIDs) by general practitioners, orthopaedic surgeons or rehabilitation specialists, which periodically suppress and mask symptoms, also contribute to delayed diagnosis, as pain relief postpones diagnostics [30]. It has also been shown that non-radiographic axial spondyloarthritis was often overlooked during diagnostics by doctors other than rheumatologists despite having the same clinical symptoms as ankylosing spondylitis [31]. In addition, it has been indicated that patients with nr-axSpA may develop r-axSpA within two years, while about 20–30% of patients may develop it within 10 years, which is another factor that may delay diagnosis [32]. It is worth mentioning that r-axSpA and nr-axSpa have the same incidence in both sexes [3]. A readily available radiological examination of the sacroiliac joints or spine detects already existing and late lesions, while an MRI, which is less accessible, detects early lesions that may be missed on an X-ray, which also delays the diagnosis [33]. In addition, test-

ing for HLA-B27 is expensive and unavailable in primary care. The presence of HLA-B27 in a patient with chronic back pain lasting longer than three months would satisfy the ASAS criteria, which would be another step in making a prompt diagnosis [34]. Due to the lack of specific tests, detection of the disease is often difficult; apart from HLA-B27, there is no specific marker for the disease. Its presence increases the likelihood of axSpA, but its absence does not guarantee the absence of the disease [35]. A family history of axSpA, even without the presence of HLA-B27, is also a significant risk factor for the development of the disease in patients with chronic lower back pain. Many studies have confirmed the high incidence of SpAy, primarily in lineal consanguinity [36]. A study conducted in Iraq by Fallshi et al. found that the longest time from symptoms to diagnosis was in patients with negative HLA-B27, low levels of education and accompanying enthesitis [37]. It has been proven that the diagnosis was more often made when anterior uveitis, young age and male sex were combined [38]. Delayed axSpA diagnosis can also be attributed to the patient being referred to a rheumatologist too late. The median time from the onset of the first symptoms to the visit to the rheumatologist is about 10 months, while from the rheumatological examination to the diagnosis is about 1 month [30]. The papers highlighted that delays in diagnosis are largely due to primary care physicians misdiagnosing patients' symptoms [39]. Because inflammatory back pain occurs in most patients, attempts have been made to construct screening tests, which could be the key to diagnosing axSpA. The Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR) strategy has been developed, which also evaluates extra-articular symptoms to help primary care physicians consider axial spondyloarthritis as a cause of back pain and guide further care, possibly referring the patient to a rheumatologist. Patients with features of typical inflammatory pain were categorised as being at risk. It was noted that in patients at risk, axial spondyloarthritis was diagnosed in up to 17–33% [40]. Simpler strategies that mainly consider lower back pain, such as the German Multicentre Ankylosing Spondylitis Survey Trial to Evaluate and Compare Referral Parameters in Early SpA (MASTER) and the US Prevalence of Axial Spondyloarthritis (PROSpA), have been shown to correctly identify axSpA patients [41, 42].

CONCLUSIONS

Axial spondyloarthritis is a chronic arthritis that causes pain and stiffness in the spine, reduces mobility and decreases quality of life. Undiagnosed patients do not receive adequate treatment and, therefore, may experience more severe symptoms, as well as adverse consequences of the disease in the future, such as disability. Both standard anti-inflammatory and biological treatments are more effective when inflammation predominates and osteoarticular changes have not formed yet. In addition, the presence of the disease itself indirectly predisposes to cardiovascular disease, sleep apnoea and depression. The disease compromises the mental health of patients, prevents them from working and causes negative economic consequences, with patients often quitting their jobs and taking sick leave and benefits.

Inflammatory lower back pain is usually the first and foremost symptom of axial spondyloarthritis, so it is essential to know its characteristics first.

Primary care physicians are the first care providers for patients with back pain and must be aware of the clinical features suggesting axSpA. This is particularly important in young patients, patients with atypical symptoms and women, as the time from symptoms' onset to diagnosis is longest in these groups. Improving awareness of axSpA, including both ankylosing spondylitis and nr-axSpA, among doctors of other specialities would facilitate faster referral of patients to a rheumatologist for early diagnosis and implementation of effective treatment. It appears that universal screening strategies that consider the main symptoms of axial spondyloarthritis could be helpful, as is the case in other countries (Germany, United States), where the diagnosis is made more quickly.

AUTHOR CONTRIBUTIONS

K.W.-W. — literature search and analysis, preparation and writing of the manuscript; E.W. — study design, approval of the final version of the manuscript, ensuring study integrity, correspondence with the Editor.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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