Causes of pain in patients with axial spondyloarthritis

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ABSTRACT

Back pain, most frequently of the inflammatory type, is the leading symptom in patients with axial spondyloarthritis (axSpA). Back pain in these patients is usually either due to axial inflammation or structural changes based on new bone formation. However, there are other possible causes of pain in these patients. There is, for example, a strongly increased risk of vertebral fractures, and, especially in patients with longstanding disease, degenerative spinal changes may play an additional role as a cause of pain. Rarely, but rather specifically, patients with ankylosing spondylitis may develop subarachnoidal cysts that often cause neurologic symptoms, in extreme cases a cauda equina syndrome. It is therefore mandatory to always carefully evaluate the origin of back pain in these patients and to consider all possible differential diagnoses. The correct diagnosis is of major importance because treatments may differ considerably. In the monitoring of patients with axSpA it is especially important to consider that pain may have a different origin and it is crucial to notice changes in the nature of the reported back pain. Accordingly, the recently updated Assessment of Spondyloarthritis international Society (ASAS)/European League Against Rheumatism (EULAR) and the treat-to-target recommendations both define improvement of symptoms, a reduction of pain and abrogation of inflammation as important targets in axSpA that can be achieved by pharmacological and non-pharmacological treatments, in rare cases including surgical methods.

Introduction

Spondyloarthritis (SpA) is a heterogeneous group of rheumatic diseases characterised by inflammatory back pain, peripheral arthritis and enthesitis, axial inflammation, joint erosions and new bone formation, especially in the spine (1). Several sub forms are differentiated: axial SpA (axSpA), psoriatic arthritis (PsA), reactive arthritis, arthritis associated with inflammatory bowel disease (IBD) and undifferentiated peripheral SpA (2, 3). In this review we focus on axSpA which includes both, classification as ankylosing spondylitis (AS) or non-radiographic axSpA (nr-axSpA). The disease course of axSpA is highly variable and often characterised by persistent or fluctuating axial inflammation as assessed by magnetic resonance imaging (MRI) and structural progression as assessed by conventional radiography. Both, inflammation and new bone formation, may lead to pain, restricted mobility, reduced function and disability leading to an impaired quality of life. Ongoing inflammation is associated with new bone formation. AxSpA is characterised by a strong association with HLA-B27 and other genes such as ERAP-1 and the IL-23 receptor. SpA is a common chronic inflammatory joint disorder, with a recently estimated prevalence of 1–2% in Caucasian populations. Typically starting in the second and third decade of life the life expectancy is decreased mainly due to cardiovascular comorbidity. Pain and disease activity may persist for several decades in life. Male gender and smoking are additional risk factors for radiographic progression. Treatment options include non-steroidal anti-inflammatory agents, biologics and physiotherapy.

Presentation of pain in patients with axial SpA in routine care

The most significant clinical symptoms are inflammatory back pain and peripheral, usually asymmetric oligoarthritis and enthesitis which are often accompanied by pain and swelling. Clinical symptoms range from isolated pain in the spine to pain in the joints caused by inflammation in the joint or in the entheses (1).

The most prevalent health-related quality of life (HRQoL) concerns include

pain and stiffness as well as fatigue and sleep problems (4). The majority of AS patients (83%) report different degrees of pain and associated problems, for one third of them stating that pain is a very important symptom (5). Women are 2-3 times more likely than men to report high levels of pain. Female patients also report smaller reductions of pain in randomised controlled trials with approved drugs (6). Furthermore, substantial fluctuations in pain can be found in individuals but on the group level the outcome measures remained constant over time (7). However, recognition of a disease flare in clinical care requiring a change in medication is influenced by several factors. As shown in a recent ASAS initiative, a change in pain or a change in Ankylosing Spondylitis Disease Activity Score (ASDAS) or the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is the most frequent definition according to a case vignette exercise (8).

Pain has a substantial impact on the life of patients in several ways. Most studies have focused on the influence of pain on physical function, some also on emotional components (9). However, the origin of back pain in patients with axSpA needs to be diagnosed individually in every patient. Back pain in patients with axSpA is commonly either due to inflammation or due to new bone formation. This differentiation can be a challenge for the treating physician because treatment approaches for the different causes of back pain may differ fundamentally (10). The interaction between inflammation and structural damage also influence physical function (10-12). Rarely, but rather specifically, patients with AS may develop subarachnoidal cysts that often cause neurologic symptoms, in extreme cases a cauda equine syndrome (13-15). Other frequent causes of back pain are vertebral fractures and disc and joint degeneration (see *Differential diagnosis*) (16, 17).

Which clinical symptoms of axSpA are important for affected patients is not well known. Recently a prospective assessment of the relative importance of aspects of health for patients with axSpA was performed, focusing on items of the ASAS Health Index (ASAS HI) (18). This disease-specific questionnaire contains items addressing categories of pain, emotional functions, sleep, sexual function, mobility, self-care, and community life (19). The five most important items are pain, sleep, exhaustion, and the ability to stand (Table I). These findings were robust and the relative importance of health aspects was similar across subgroups of patients (disease subgroups AS / nr-axSpA, age, disease duration, work status and disease activity). Similar levels of pain in patients with AS as well as in nr-axSpA patients was also found to be present in another prospective cohort some years ago (20). While both groups do not differ regarding health status, disease activity and physical function, they do differ in signs of inflammation – all were higher in patients with AS.

Inflammatory back pain

The most characteristic symptom of axSpA is chronic back pain, frequently of inflammatory nature (IBP), which is clinically well defined (21-23). However, since the sensitivity and specificity of IBP for diagnosis and classification of axSpA is limited, the combination of chronic back pain lasting >3 months and onset of typical symptoms before the age of 45 years have been chosen for classification criteria and referral recommendations (24, 25). Indeed, the sensitivity of IBP for a diagnosis of AS has been shown to be about 70% (21). In the ASAS classification criteria for axial SpA IBP is on the list of items indicative of axSpA (25).

Patients with IBP complain about morning stiffness (>30 minutes duration), insidious onset of back pain, awakening because of back pain during the second half of the night and alternating buttock pain. Many patients report that pain improves by movement rather than by rest and the proportion of patients who have significant benefit from non-steroidal anti-inflammatory drugs (NSAIDs) is considerably higher than in those with non-specific low back pain (22). The following items have been shown to be relevant in that regard:

- duration - >3 months
- age at onset - <45 years (or younger)
- localisation - lower back
- mode of onset - insidious
- inflammatory - morning stiffness >30 minutes
- time - wakening up in the 2nd half of the night
- response to intervention - improvement by movement, not by rest

These items are used as sets for diagnosis and preselection of patients to optimise referral processes (26). The definitions of IBP used in these criteria sets are variable, and views on the clinical usefulness, sensitivity and specificity of the items are contradictory (Table II). However, no single parameter has shown the ability to differentiate the various possible reasons for back pain (27). IBP is more often present in patients with AS compared to patients with other forms of SpA (28). Because back pain is such a common symptom in patients presenting in the offices of general practitioners (GPs) and orthopedic surgeons, IBP is not only important to rheumatologists (29). However, the diagnostic value of the IBP criteria sets has been evaluated in specialised rheumatology care. Since the perception of IBP in GP care is weak it can be hypothesised that the diagnostic value of the IBP criteria sets in GP care is even much lower (30). In addition, the performance of IBP criteria sets differ between GP's and rheumatologist's offices because the pretest probability of axial SpA is relatively low in primary care, as compared to a more specialised care.

When talking about differential diagnosis, referral of patients to the respective specialists is an important topic, since back pain is a frequent complaint and the capacity of rheumatologists to see patients with back pain in general for screening purposes is limited. Therefore, preselection of patients is very important. Several referral systems for considering a rheumatologic consultation have been proposed. The simplest one that has been developed on a data driven basis concentrates on just three items: buttock pain, improvement of the pain by movement and occurrence of psoriasis at any time point

Table I. Relative importance of health represented in the ASAS Health Index (ASAS HI).

Item of the ASAS Health Index	Aspect	Relative importance		Number of patients (of 192) with problems (%)
		Mean score	95%-CI	
Pain sometimes disrupts my normal activities	Pain	14.20	(13.80 to 14.60)	157 (78.9%)
I sleep badly at night	Sleep	10.28	(9.59 to 10.96)	113 (56.8%)
I am often exhausted	Being exhausted	9.63	(9.01 to 10.25)	115 (57.8%)
I find it hard to stand for long	Standing	9.25	(8.53 to 9.98)	142 (72.1%)
I am less motivated to do anything that requires physical effort	Motivation	8.70	(8.05 to 9.34)	110 (55.3%)
I often get frustrated	Frustration	6.05	(5.42 to 6.67)	86 (43.2%)
I have problems running	Running	5.88	(5.10 to 6.70)	131 (65.8%)
I have experienced financial changes because of AS	Financial changes	5.45	(4.67 to 6.22)	88 (44.2%)
I am restricted in traveling because of my mobility	Travel	5.30	(4.65 to 5.95)	83 (41.7%)
I cannot overcome my difficulties	Be able to overcome difficulties	4.82	(4.23 to 5.41)	56 (28.1%)
I find it hard to concentrate	Concentration	4.42	(3.81 to 5.03)	64 (32.2%)
I am not able to walk outdoors on flat ground	Walking outdoors	3.89	(3.37 to 4.41)	40 (20.1%)
I lost interest in sex	Sexual relationships	3.20	(2.65 to 3.74)	52 (26.1%)
I have problems using the toilet	Toileting	3.17	(2.58 to 3.75)	49 (24.6%)
I am finding it hard to make contact with people	Contact with people	2.36	(1.89 to 2.82)	33 (16.6%)
I have difficulty operating the pedals in my car	Driving	1.78	(1.39 to 2.17)	26 (13.1%)
I find it difficult to wash my hair	Washing hair	1.63	(1.25 to 2.01)	28 (14.1%)

Table II. Variables of different definitions for IBP.

	Calin A *et al*.: first historical definition [23]	Rudwaleit M *et al*.: Based on study data [21]	Sieper J *et al*.: Based on expert consensus [22]
Age at onset	<40 years	<45 years	≤40 years (odds ratio (OR): 9.9)
Duration	≥3 months	≥3 months	
Onset	insidious		insidious (OR: 12.7)
Clinical features	Morning stiffness	Morning stiffness > 30 minutes	
Response to interventions	Improvement by movement		Improvement by movement (OR: 23.1)
		No improvement by rest	No improvement by rest (OR 7.7)
		Alternating buttock pain	
		Wakening up in the 2nd half of the night	Night pain (OR: 20.4)
Sensitivity[#]	If 4/5 criteria: 90%	if 2/4 criteria: 70%	if 4/5 criteria: 80%
Specificity[#]	if 4/5 criteria: 52%	if 2/4 criteria: 81%	if 4/5 criteria: 72%

[#] Data of the Validation cohort (n=648) as reported in (ref. 22).

(31). If less than 2 of these items are present, determination of HLA B27 is recommended prior to referral to the rheumatologist. This proposal is currently being evaluated in a larger study.

Differential diagnosis based on pain in patients with axSpA

The correct diagnosis of axSpA including the differentiation of the many different causes of back pain is of major importance because treatments may differ considerably (Table III). However, the differential diagnosis of back pain in an unselected patient group may be challenging. When presenting in a primary care setting, only a small proportion of patients will have axial inflammation as the major cause of their back complaints (32). Numerous diseases such as degenerative disk disease, degenerative changes in the intervertebral (facet) joints and the associated ligaments, spinal instability, herniation of the intervertebral disk, spinal stenosis and hypermobility have to be considered and interpreted together with imaging of the spine (33). A recent study from the Netherlands showed that the prevalence of degen-

Table III. Causes of back pain in patients with SpA.

Axial inflammation including sacroiliitis, spondylitis, spondylodiscitis, enthesitis
Structural damage (new bone formation, ankylosis, hyperkyphosis)
Vertebral fractures
Spinal instability due to atlantoaxial dislocation
Subarachnoidal cysts
Degenerative spinal changes
Disc herniation
Spinal stenosis
Fibromyalgia, myofascial pain syndromes
Muscular dysbalance
Non-specific (low) back pain
All other causes of back pain (myocardial infarction, aneurysm, pleuritis, paptic ulcer, etc.

erative changes in the spine is similar in patients with SpA and no SpA, especially in patients with younger age (16). This is one reason why the diagnosis of axSpA is often delayed, as symptoms can be confused with other more common but usually less serious disorders such as chronic low back pain (34). Pain in patients with SpA is not only present as back pain but also as widespread pain which can mislead to the diagnosis of fibromyalgia (FM) (35). Similarly, patients with FM may also present with chronic back pain, morning stiffness and functional impairment, which may be a challenge for a diagnostic differentiation to axSpA (36). It has been shown that patients with axSpA fulfill ASAS classification criteria for axial SpA and in a quarter also the FM classification criteria, but that FM patients in most cases did not fulfill ASAS classification criteria for axial SpA (37) (Rheumatology 2017, accepted). In this context it is important to understand that patients with axial and/or peripheral pain might suffer from an enthesitis as well, since these issues presence can easily be overlooked in a clinical setting (38). The disease course in patients with axSpA can be complicated by an increased risk of vertebral fractures which adds another aspect of pain aetiology in patients with an established disease (39). Many fractures are missed in clinical setting because back pain has been interpreted as a disease flare of spondylitis (40). Moreover, the fact that more AS patients with syndesmophytes had reduced bone density than those without suggests that bone growth and bone loss occur in parallel in axSpA patients (41).

Assessment of pain in patients with SpA

As already mentioned, pain and especially back pain is one of the major symptom of patients with SpA. ASAS/ EULAR management recommendations focus primarily on reducing and controlling signs and symptoms and therefore maximising health-related quality of life by preventing progressive structural damage and preserving/ normalising function and social participation (42). ASAS recommends individualising the treatment of patients with axSpA according to the current signs and symptoms of the disease (axial, peripheral, extra-articular manifestations). The assessment of pain, patient global and physical function is recommended as core domains in clinical record keeping according to ASAS/ Outcome Measures in Rheumatology (OMERACT) (43). In the monitoring of patients with axSpA it is especially important to consider that pain may have a different origin and it is crucial to notice changes in the nature of the reported symptoms of back pain. Therefore, assessment of pain is crucial in the management of patients with axSpA. Pain as a single measure can be assessed by using a numerical rating scale (NRS) or visual analogue scale (VAS) for pain in general or for spinal pain in particular. Most disease activity instruments also include a question about pain. Different types of disease activity measures are available: self-report (patient) instruments (*e.g.*, BASDAI and composite indices (*e.g.*, ASDAS) (44, 45). The patients should report the level of back pain and level of pain in the joints, overall level of fatigue and morning stiffness. The 6 items of the BASDAI sum up to a score between 0–10, higher values indicate more active disease. However, it is well known that the BASDAI is a subjective measure based on patient's perceptions reporting their pain at different locations, its duration and intensity, the extent of morning stiffness and the overall level of fatigue. The composite index Ankylosing Spondylitis Disease Activity Score (ASDAS) is using three questions of the BASDAI (Question 2 about total back pain, Question 3 about peripheral pain and Question 6 about morning stiffness) but also inflammatory markers (C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)) and patient' global assessment. ASDAS was shown to be highly discriminatory in differentiating patients with different levels of disease activity (46).

Treatment

Improvement of pain can be achieved by pharmacological, surgical and non-pharmacological therapies. Several trials showed a reduction of pain and preservation or amelioration of function when AS patients performed regular exercises (47). However, the effect size was moderate and improvements didn't last for longer periods of time. NSAIDs and biologics have demonstrated efficacy and efficiency including reduction of pain in patients with axSpA. If taken in proper dosages, NSAIDs are efficacious and relief pain and stiffness in 70–80% of patients (48). A meta-analysis of trials investigating the effect of NSAIDs showed a high effect size for the domain pain (1.07), but only a medium effect size for the domain physical function (0.54) (49, 50). The role of analgesics has not been formally studied so far. According to the ASAS recommendations, analgesics such as paracetamol might be considered for residual pain in axSpA patients after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated (42).

The introduction of tumour-necrosis-factor inhibitors (TNFi) has clearly opened a new era of treatment of patients with axSpA. TNFi show strong therapeutic effects in both, peripheral and axial SpA. Anti-TNF therapy leads to a marked reduction of pain and improvement of function, as shown in many clinical trials and different meta-analyses (49-51). For the domains pain and patient's global assessment, the treatment effect for TNFi was large (standardised mean difference (SMD) (95% confidence interval (CI)) -0.9 (-1.07, -0.73)) (49). Patients treated with TNFi were more likely to achieve an ASAS 20 response after 12 weeks in all randomised controlled trials (RCTs) performed so far in axSpA (52). A marked pain reduction as assessed by ASAS 20 or BASDAI50 response rates was also seen in trials with the interleukin-17A inhibitor secukinumab in AS (53, 54).

Improvement of symptoms and reduction of pain can be achieved not only by pharmacological and non-pharmacological treatments, but also with surgical methods in patients with severe hip involvement or spinal hyperkyphosis. In patients with refractory pain and/or

disability and radiographic evidence of structural damage, independent of age, ASAS recommends to consider a total hip arthroplasty and in patients with severe disabling deformity a spinal corrective osteotomy to be performed in specialised centres (42). Although scientific evidence is much lower compared to pharmacological treatment options, reduction in pain and improvement in function has been described in retrospective case series (55-57). Reduction of pain has been reported for surgical treatment of spinal fractures as well, although the main intention for this intervention is to prevent neurologic complications (17, 58).

Conclusion

Major improvements have been made to understand pain as a multifaceted complain in patients with axSpA. Pain is the hallmark feature of axSpA clinically but it is important to recognise that patients with axSpA also have peripheral and even widespread pain. Pain is also the most important symptom for patients with axSpA when compared to other factors such as sleep, fatigue and frustration. NSAIDs and biologics are the key pharmacologic therapies for axSpA as they can lead to significant reductions in pain and disease activity. However, monitoring of the intensity and type of pain requires special attention during the disease course because axSpA patients also develop non-inflammatory types of pain from factors such as degenerative changes or vertebral fractures.

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