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Review

Comorbid pain in axial spondyloarthritis, including fibromyalgia

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***Abstract*:** The main symptom in patients with axial spondyloarthritis (axSpA) is inflammatory back pain, caused principally by inflammation of the sacroiliac joints and the spine. However, not all back pain in patients with axSpA is related to active inflammation: other types of pain can occur in these patients, and may be related to structural damage (e.g. ankylosis), degenerative changes, vertebral fractures or comorbid fibromyalgia, which are not uncommon in these patients. Structural damage and ankylosis may lead to a biomechanical stress, which can lead to chronic mechanical pain; and degenerative changes of the spine may also exist in patients with axSpA also leading to mechanical pain. Osteoporosis is more prevalent in axSpA patients than in the general population, and vertebral fractures may result in acute bone pain, which can persist for several months. Fibromyalgia, which is also more prevalent in patients with chronic inflammatory diseases (including axSpA), presents with widespread pain which can mimic entheseal pain. A correct diagnosis of the origin of the pain is crucial, since treatments and management may differ considerably. Recognizing these causes of pain may be a challenge in clinical practice, especially for fibromyalgia, which can coexist with axSpA and may have a significant impact on biologic drug response.

In this review, we provide an update of the most common causes of pain other than inflammatory back pain in axSpA patients, and we discuss the latest management options for such causes.

Keywords: fibromyalgia, pain, spondyloarthritis

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Introduction

Spondyloarthritis (SpA) is a chronic inflammatory disease that mainly affects the axial skeleton (spine and sacroiliac joints), peripheral joints and enthesis.[1] Patients with predominantly axial symptoms can be classified as axial spondyloarthritis (axSpA), which encompasses patients with radiographic axSpA (r-axSpA, with advances structural damage on X-ray) and nonradiographic axSpA (nr-axSpA, no definitive signs of structural damage on X-ray).[2] The hallmark symptom in patients with axSpA is inflammatory back pain (IBP), which is caused principally by inflammation of the sacroiliac joints and spine. This symptom has been well defined, and it is characterized by insidious onset, morning stiffness, improvement by movement, awakenings because of back pain during the second half of the night and good response to nonsteroidal anti-inflammatory drugs (NSAIDs).[3–5] However, other type of axial pain may be related to syndesmophytes, ankylosis, vertebral fractures and degenerative changes, which are common in patients with long-standing axSpA. Other rare causes with possible neurological signs are subarachnoid cysts and atlanto-axial dislocation.[6] Furthermore, fibromyalgia (FM) can frequently be associated with axSpA, representing diagnostic and treatment dilemmas because some clinical features of axSpA (e.g. pain at enthesis) can be also found in patients with FM.[7]

Determining the cause of pain other than inflammation in axSpA patients may be challenging in clinical practice.

Syndesmophytes and ankylosis

Axial SpA is characterized by local inflammation in the enthesis at the annulus-bone junction or in

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the subcortical vertebral body, causing new bone formation and the development of syndesmophytes, resulting in vertebral fusion and ankylosis.[8,9] Patients with long-standing axSpA show a gradual loss of the normal lumbar lordosis, often associated with spasms of paraspinal muscles which become tender.[10] Moreover, the excessive kyphosis of the thoracic spine observed in these patients may lead to a biomechanical stress producing chronic pain. Kyphosis produces an excessive stress on the ligaments and muscles of the thoracic spine producing local pain.[11] However, these patients may also experience inflammatory pain despite total ankylosis of the spine. In fact, van der Heijde *et al.* reported that patients with a total spinal ankylosis may also have active inflammatory disease and that the symptoms of active disease in these patients can be improved with anti-tumour necrosis factor (TNF)-α treatment.[12]

Degenerative changes

Magnetic resonance imaging (MRI) plays a key role in the diagnosis and evaluation of axSpA patients. MRI can show not only bone marrow oedema but also structural lesions for axSpA, such as fatty lesions, erosions and bone formation.[13] Apart from these lesions, MRI may also detect degenerative changes, which either occur in isolation or in combination with typical lesions for axSpA.[14] These degenerative changes might be mistaken for inflammatory lesions as sometimes they can be present with bone marrow oedema. It has been described that up to 70% of patients with recent axSpA show at least one degenerative lesions of the spine, concentrated predominantly in the lower lumbar spine.[14] The most frequent finding was degenerated discs (42.9%) (i.e. degenerative complex with the presence of disc degeneration and a high-intensity zone and herniation together in an intervertebral discs) and Schmorl nodes (36.7%) (i.e. projection of disc material into the vertebral endplate, resulting in an indentation of the vertebral endplate), while Modic type I and II changes were exceptions. Modic type I lesions, herniation (projection of disc material outside the vertebral contour), high-intensity zone and degenerative disc disease have shown a strong association with pain, being strongest in patients >35 years old.[13] Treatment for patients with mild to moderate pain is conservative and includes analgesics (i.e. acetaminophen or NSAIDs), neuropathic pain medication in case of radicular symptoms and opioids.[15] Epidural steroid injections can be proposed in patients with radicular pain from herniated discs in patients who do not respond to conventional treatment.[15]

Vertebral and spinal fractures

Osteoporosis is the most frequent comorbidity among patients with SpA, with a prevalence of 13.4%.[16] Despite excessive bone formation in axSpA, these patients have a high risk of vertebral fracture (VF) due to the combination of low bone mineral density (BMD) and mechanical factors related to stiffening of the spine.[6,17] Increasing evidence suggests that changes in the biomechanical properties of the spine such as osteoporosis (rending the vertebrae prone to fracture) and osteoproliferation (making the spine less flexible) play an intermediate role.[17]

The prevalence of VFs among the axSpA population has been reported to be between 6% and 20%, depending on the cohort.[18–21] However, this prevalence is even lower in recent axSpA cohorts, in which this prevalence is approximately 3.0% with an incidence of new VF of 1.1% over 5 years of follow up.[22] The majority of VFs in these patients are located at the thoracic spine, which is also the most frequent location of vertebral deformities (due to anterior corner erosions, squaring and wedging).

Despite the observation that >80% of VFs are asymptomatic in patients with axSpA,[23] sometimes they may result in bone pain and muscle spasm, and disabling pain can persist for several months.[24,25] Short-term bed rest and pain relief with acetaminophen and NSAIDs can be used as general measures; however, long-term therapy with calcitonin is not recommended. Spinal orthoses and corsets should be considered in the acute treatment phase to help immobilize the fracture site, reducing loads on fractured vertebrae and improving spinal alignment.[25,26] Physical therapy, such as ultrasound, hydrotherapy, early mobilization and stretching exercises, may be beneficial to patients in reducing pain and improving mobility.[25]

The management of chronic pain due to a long-standing VF may be a challenge, as these patients may experience chronic back pain related to degenerative changes adjacent to the VF. Moreover, due to the kyphosis, the biomechanics of the spine may be disrupted resulting in chronic

soft-tissue pain.[25] In case of persistent and severe pain, a vertebroplasty can be proposed, even if the role of vertebroplasty for treating acute or subacute osteoporotic vertebral fractures in routine practice is controversial.[27]

Spinal fractures (e.g. trans-discal fractures) are a different entity from VFs, as they are not related to low BMD. They can occur after a trauma in patients with an ankylosed spine, being their hallmark an injured posterior osteoligamentous component detected in MRI or in computerized tomography.[28] Direct compression by the fracture or by spinal epidural haematoma can lead to spinal cord injuries, necessitating urgent neurosurgical intervention. Moreover, subacute myelopathy can also occur with focal narrowing of the canal due to plane deformation after a displaced spinal fracture.[28]

Cauda equina syndrome and atlantoaxial subluxation

Neurological complications in axSpA patients are uncommon. Cauda equina syndrome is a rare but significant complication of long-standing axSpA patients.[10] It manifests clinically as sciatic pain in 22% of patients, low back pain in 10%, weakness in 62%, sensory loss in 96%, bladder dysfunction in 95% and bowel disfunction in 80%.[29,30] The pathophysiology is thought to include arachnoiditis and chronic dural inflammation, which may result in dural ectasias. Another hypothesis is that a reduced compliance and an expansible caudal sac resulting from excessive cerebrospinal fluid pressure lead to a capacious caudal sac, enlarging arachnoid diverticula, secondary erosion into bone and potential lumbosacral nerve root injury.[23,31] Myelography and MRI show a wide spinal canal without compressive lesions but with posterior lumbosacral arachnoidal diverticula.[10] Rheumatologists should consider cauda equina syndrome in patients with long-standing axSpA who have slowly progressing sensory and motor symptoms affecting the lower limbs with sphincter dysfunction.[30] Treatments for this syndrome include NSAIDs, corticosteroids, acetazolamide, lumbo-peritoneal shunting and laminectomy. These surgical procedures may improve or stop the neurological deterioration, but both procedures have significant risk of complications in patients with ankylosed spine.[29]

Spontaneous atlantoaxial subluxation is a well-recognized complication in patients with rheumatoid arthritis. However, approximately 2% of patients with axSpA may show this complication, presenting with or without signs of spinal cord compression.[23] Duration of the disease is the major factor that determines atlantoaxial subluxation, but it is also associated with the presence of peripheral arthritis.[32] One possible explanation is that chronic systemic inflammation in these patients may lead to chronic synovitis resulting in bony erosion and ligamentous laxity that may result in instability.[33] Other causes of atlantoaxial subluxation may be sequelae of ossification of the anterior and posterior longitudinal ligaments and physical stresses (kyphosis of the dorsa spine and weight of the head at the C1–C2 level).[23] One of the most common symptom of atlantoaxial subluxation is neck pain at the C1–C2 or occipital level. Patients presenting with this condition can also suffer from paraesthesia, weakness or signs of myelopathy upon examination.

Management of atlantoaxial subluxation in rheumatic patients includes patient education, lifestyle modification, regular radiographic follow up and early surgical intervention when indicated.[33] Aggressive drug treatment with disease-modifying antirheumatic drugs in combination with TNF-α inhibitors administered before the onset of cartilage destruction reduces the incidence of upper cervical abnormalities.[33,34]

Fibromyalgia

FM is a chronic condition characterized by widespread pain, which is the dominant symptom, associated with fatigue, nonrefreshed sleep, mood disturbance and cognitive impairment.[35] In the last few years, FM has been considered a comorbid condition in patients with rheumatic diseases, that is, coexistent clinical disorders that appear as a consequence of persistent inflammatory activity and/or treatment.[36] The prevalence of FM in the general population ranges from 2% to 7%, while it has been reported to be more frequent in patients with inflammatory rheumatic diseases. In axSpA patients specifically, it has been reported to have a prevalence of 25%.[37,38] However, this prevalence can be different depending on the use of different FM criteria. A recent study demonstrated that the prevalence of coexistent FM using the 2010 criteria was significantly higher than that using the 1990 criteria (24% *versus* 14%, respectively) in the same cohort.[39] Interestingly, Moltó *et al.* demonstrated that the prevalence using the Fibromyalgia Rapid Screening Tool (FiRST)

questionnaire[40] was even higher (37.8%), suggesting that concomitant FM is more frequent in axSpA patients than the general population but not more frequent than in other rheumatic diseases.[41]

Several studies have demonstrated that FM in axSpA patients is associated with peripheral enthesitis and the female sex.[41] FM is characterized by widespread pain and tenderness, which can be caused by enthesitis, present in up to 55.8% of patients with recent axSpA.[42] In fact, a significant degree of overlap between FM tender points and enthesitis sites in patients with IBP have been demonstrated.[43] Similarly, many FM patients can also suffer from spinal morning stiffness and they could fulfill IBP. For this reason, in 2018, a consensus-based definition of ultrasound-detected enthesitis in SpA and psoriatic arthritis (PsA) was published, which allows for its differentiation from noninflammatory enthesitis.[44] Interestingly, although nr-axSpA patients have shown a greater prevalence of enthesitis in comparison with r-axSpA,[45] the prevalence of coexistent FM using both the 2010 and the 1990 criteria was demonstrated to be more frequent in r-axSpA than in nr-axSpA, showing that nr-axSpA patients are not especially prone to have FM compared to patients with r-axSpA.[39] These results were confirmed in a French cohort in which an association between FM according to the FiRST questionnaire and absence of radiographic sacroiliitis was not found.[41]

Axial SpA patients presenting with concomitant FM exhibit higher scores for patient-reported outcomes (PROs) such as the Bath Ankylosing Spondylitis Activity Index (BASDAI).[46] Moreover, a definition based on "extreme PRO" has been validated as a surrogate marker of FM in axSpA in which the specific instruments for FM recognition are not available.[47] Interestingly, patients fulfilling the "extreme PRO" definition had similar characteristics as FM patients; they were frequently women, older and with a history of depression or antidepressants drugs use.[46] Axial SpA patients with concomitant FM also usually report significantly worse function, global severity scores and poorer quality of life.[48] For this reason, objective measures, such as C-reactive protein (CRP), and the Ankylosing Spondylitis Disease Activity Score play a key role in discriminating between pain caused by inflammatory activity and pain due to the interference of FM.[49]

The evaluation of FM in axSpA patients is of particular interest since the coexistence of this comorbidity impacts treatment and patient management. Because axSpA patients with concomitant FM usually present with higher scores on PROs, the evaluation of disease activity and treatment effect might be challenging and might lead to unnecessary initiation of biologic disease-modifying antirheumatic drugs (bDMARDs), dose escalations and switches.[50] In 2016, Bello *et al.* demonstrated that the percentage of patients initiating bDMARDs was similar between FM^+ and FM^- patients; however, patients with concomitant FM were more likely to switch to other bDMARD treatments and the retention rate for the first bDMARD agent was shorter in the FM group.[50] These results suggested that FM should be screened for axSpA patients when initiating anti-TNF and/or evaluating its treatment effect, especially in the presence of peripheral and/or enthesitic symptoms and in the presence of extreme PROs. Later, a study conducted by Moltó *et al.* showed that concomitant FM has a significant impact on anti-TNF response after 12 weeks of follow up, but the impact was only observed when this effect is evaluated by PROs and not by objective biological parameters (i.e. CRP).[41] In the same line, Iannone *et al.* recently reported a significantly lower drug survival in psoriatic arthritis patients with concomitant FM, as well as lower rate of remission after 24 months of follow up.[51]

Management of fibromyalgia

Patients with FM should be managed according to the European League Against Rheumatism revised recommendations published in 2017.[52] The overarching principles of these recommendations are, first, to comprehensively assess pain, function and psychosocial context; and, second, to objectively manage FM to improve health-related quality of life using a multidisciplinary approach that combines pharmacological and nonpharmacological treatment modalities. The management of FM comprises different steps. First, the use of exercise is strongly recommended, given its effect on pain, physical function and well-being (without distinction between aerobic or anaerobic exercise). Meditative movement therapies or mindfulness-based stress reduction are also recommended, since they improve sleep and quality of life, as well as physical therapies (acupuncture or hydrotherapy).

Hypnotherapy, massage and other alternative therapies are not recommended because of a lack of effectiveness. When patients do not respond to nonpharmaceutical treatments, pharmacological therapies should be considered, especially for patients with severe pain (tramadol, pregabalin, duloxetine) or sleep disturbance (amitriptyline, cyclobenzaprine, pregabalin). NSAIDs, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors and strong opioids are not recommended because of a lack of efficacy and risk of side effects.

Conclusion

Pain is the hallmark feature of axSpA, but it is important to recognize types of pain other than related to inflammation. Other causes of pain may be ankylosis, degenerative changes, vertebral fractures and FM. Determining the cause of pain in axSpA patients is crucial in clinical practice, as each patient will require a specific treatment.

Conflict of interest statement

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