

Chronic widespread pain in spondyloarthritis

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SUMMARY

The pain associated with spondyloarthritis (SpA) can be intense, persistent and disabling. It frequently has a multifactorial, simultaneously central and peripheral origin, and may be due to currently active inflammation, or joint damage and tissue destruction arising from a previous inflammatory condition. Inflammatory pain symptoms can be reduced by non-steroidal anti-inflammatory drugs, but many patients continue to experience moderate pain due to alterations in the mechanisms that regulate central pain, as in the case of the chronic widespread pain (CWP) that characterises fibromyalgia (FM). The importance of distinguishing SpA and FM is underlined by the fact that SpA is currently treated with costly drugs such as tumour necrosis factor (TNF) inhibitors, and direct costs are higher in patients with concomitant CWP or FM than in those with FM or SpA alone. Optimal treatment needs to take into account symptoms such as fatigue, mood, sleep, and the overall quality of life, and is based on the use of tricyclic antidepressants or selective serotonin reuptake inhibitors such as fluoxetine, rather than adjustments in the dose of anti-TNF agents or disease-modifying drugs.

Key words: Spondyloarthritis, Fibromyalgia, Prevalence, Disease activity, Ankylosing spondylitis disease activity score, Bath ankylosing spondylitis disease activity index.

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INTRODUCTION

Spondyloarthritis (SpA) refers to a family of diseases with a number of common clinical features (1). The most distinguishing are axial joint inflammation, asymmetric oligoarthritis, dactylitis and enthesitis, but others include genital and skin lesions, eye and bowel involvement, an association with current or previous infection, and a close correlation with human leukocyte antigen (HLA) B27 (2, 3).

The pain associated with SpA can be intense, persistent and disabling (4, 5). It frequently has a multifactorial, simultaneously central and peripheral origin (6), and may be due to currently active inflammation, or joint damage and tissue destruction arising from a previous inflammatory condition (7). Inflammatory pain symptoms can be reduced by non-steroidal anti-

inflammatory drugs (NSAIDs), but many patients continue to experience moderate pain (8, 9) due to alterations in the mechanisms that regulate central pain, as in the case of the chronic widespread pain (CWP) that characterises fibromyalgia (FM) (10). The many complex mechanisms giving rise to CWP include temporal summation (wind-up), long-term potentiation (LTP), heterosynaptic potentiation, dysfunctional descending pain inhibition, and activation of the descending facilitatory pathway (11). Experimental studies of sensitivity to pain have shown that the pressure eliciting pain (also known as the pressure pain threshold or PPT) is lower in patients with rheumatoid arthritis (RA) than in healthy controls (6). The fact that this is true at articular and non-articular sites suggests that the widespread pain associated with RA is mediated by changes in the mechanisms regulating

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central pain, such as central sensitisation and a lack of conditioned pain modulation. Incel et al. studied 17 Ankylosing Spondylitis (AS) patients, 20 RA patients, and 21 healthy volunteers, and found that the PPTs of the RA patients (but not those with AS) were significantly lower than the PPTs of healthy volunteers (12). However, other studies have shown that widespread pain conditions such as FM significantly increase AS disease activity. The growing evidence that there is an association between FM and SpA increases the need to distinguish their clinical features because the evaluation of SpA can be complicated by the presence of FM (13-16). The main cause of diagnostic confusion relating to the 1990 American College of Rheumatology (ACR) criteria (17) is the overlap of enthesitis in SpA with the tender points (TPs) of FM. TP counts were therefore replaced by patient self-assessment in the 2010 ACR diagnostic criteria for FM (18), but this has not necessarily made them any less confusing (19). The two conditions have many similarities. SpA is diagnosed on the basis of the presence of inflammatory chronic back pain and morning stiffness (20, 21), but these are often encountered in FM patients. Furthermore, the typical characteristics of FM (fatigue, depression, anxiety and sleep disturbances) (22) are also significant aspects of AS, and are closely associated with pain, particularly in women (21). Such similarities not only lead to diagnostic problems, but may also make it more difficult to interpret treatment failure or disease relapse (23). Consequently, it has been suggested that SpA and FM can best be differentiated by means of the power Doppler ultrasound (PDUS) investigation of enthesitis (24), although this is not universally available in everyday clinical practice (25, 26).

■ THE IMPACT OF CWP ON DISEASE ACTIVITY INDICES

Disease activity indices are often used in patients with SpA (27, 28), and the good

correlation between the presence of CWP or FM and the self-reported indices of AS (including the Bath Ankylosing Spondylitis Disease Activity Index, BASDAI) (29) suggests that the CWP frequently observed in women with inflammatory rheumatic diseases may also be frequent in women with axial SpA. This may cause diagnostic delays, and could provide a further explanation for the finding that, at any given level of radiographic damage, women's self-reported functional limitations are worse than those of men. As women with primary FM have much higher BASDAI scores than women with AS (23), BASDAI may not be a good means of assessing inflammatory disease activity in SpA patients.

Patients with concomitant AS and FM are more functionally impaired, and have higher BASDAI and Ankylosing Spondylitis Functional Index (BASFI) scores than those of patients with either disease alone (30). The prevalence of FM in one study of 71 patients with AS was 15% (45.5% males and 54.5% females), and these patients all had significantly higher BASDAI, BASFI and Ankylosing spondylitis quality of life (ASQoL) scores (31). Furthermore, a cross-sectional Spanish study of 462 patients with definite AS found that their BASDAI, BASFI and total Bath AS Radiology Index (BASRI) scores were all greatly affected by the presence of FM, which distorted the measures of disease activity and functional damage (32).

Another cross-sectional study has found that FM is also frequent in axial SpA, and once again more prevalent in female patients (33). Having can worsen the symptoms of disease activity, affect function, and compromise the quality of life: as the Ankylosing Spondylitis Disease Activity Score (ASDAS) includes markers of inflammation markers it may be more useful than BASDAI in clinical practice.

One study of 547 patients in the Scotland and Ireland Registry for Ankylosing Spondylitis (SIRAS) (34) used four-view body manikins to obtain information concerning CWP not only on the basis of the 1990 ACR criteria for FM (ACR-CWP: i.e. chronic pain for >3 months in two contra-

lateral body quadrants, plus axial pain), but also on the basis of an alternative definition (aCWP) that required chronic pain in two contralateral body quadrants, but excluded pain in the axial skeleton and/or buttocks because it was felt that spinal disease would greatly affect the reporting and complicate the interpretation of the results. It was found that the age- and gender-adjusted prevalence of aCWP in AS was almost three times higher than in the general population, and was related to both individual and clinical factors (34).

■ CWP AND PSORIATIC ARTHRITIS

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy of unknown etiology whose various manifestations include mono-oligoarthritis (an erosive polyarthritis that indistinguishable from RA) and spondyloarthropathy with axial involvement or enthesitis, and affect up to one-third of psoriatic patients (35). Although the real prevalence of CWP in PsA patients is unclear, one study found tenderness in ten or more fibrotic sites in 24% of patients with PsA and 57% of RA patients (36). If there are no objective signs of enthesial inflammation, it can be difficult to distinguish enthesitic and CWP clinically, because the symptoms and signs may be aspecific. However, univariate analysis of a cross-sectional study of 266 patients with PsA and 120 with FM (37) showed that the latter had higher mean TPs and enthesitis scores, more somatic symptoms, and responded less to NSAIDs, and multivariate analysis showed that the presence of ≥ 6 FM-associated symptoms and ≥ 8 TPs was the best predictor of FM. The authors concluded that PsA and FM have some common clinical features, but that the number of FM-associated symptoms and the number of TPs were the most useful variables distinguishing FM.

As in the case of RA, the inflammation affecting different tissues in PsA patients can be detected and characterised early by means of ultrasonography, which is useful for the differential diagnosis.

■ TREATMENT OF PATIENTS WITH SPA AND CONCOMITANT CWP

Although challenging, it is important to identify CWP in SpA patients because it can have a considerable impact on their health-related quality of life, and is associated with high rates of use of healthcare resources (38-40). The difficulties in everyday living activities reported by patients with CWP or FM are as severe as those reported by patients with RA (41), and more severe than those reported by patients with osteoarthritis or other painful conditions (42, 43). The general level of well-being of FM patients referred to a specialist is lower than that of patients with AS, and they are also more expensive to treat (44). However, the direct costs of treating concomitant SpA (which is currently treated with costly tumour necrosis factor (TNF) inhibitors) and CWP or FM are higher than those of treating FM or SpA alone (45).

It is particularly important to recognise the presence of concomitant CWP in patients with chronic structural diseases in order to ensure their optimal management. Anti-TNF drugs are ineffective in patients complaining of pain even when inflammation is effectively controlled, and this can lead to unnecessary changes in treatment or dose escalations.

Treating CWP in SpA patients is particularly challenging because little is known about its etiology and the patients respond poorly to conventional treatments: for example, NSAIDs alone have no effect on CWP caused by central sensitisation, and are probably unlikely to be effective in SpA patients (8, 9).

Controlled studies have shown that tricyclic antidepressants (e.g. amitriptyline), selective serotonin reuptake inhibitors (e.g. fluoxetine), and dual serotonin and norepinephrine inhibitors (e.g. venlafaxine, milnacipram and duloxetine) can relieve pain and improve the quality of life patients with FM (46, 47).

The most widely accepted and beneficial forms of non-pharmacological therapy seem to be physical exercise and multi-

modal cognitive behavioural therapy (46, 47). However, as no single pain treatment is ideal, it is recommended to adopt an approach based on combined treatments.

■ CONCLUSIONS

Chronic widespread pain in SpA or PsA does not increase overall mortality but negatively affects the patients' quality of life, and its presence should be recognised by rheumatologists. Mechanism-based pain management should consider its simultaneous peripheral and central origin, including the effects of inputs from the brain and the descending inhibitory pathways, and optimal therapy should take into account symptoms such as fatigue, mood and disturbed sleep.

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