



Original article

Chronic musculoskeletal pain in chronic fatigue syndrome: Recent developments and therapeutic implications

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Abstract

Patients with chronic fatigue syndrome (CFS) experience chronic musculoskeletal pain which is even more debilitating than fatigue. Scientific research data gathered around the world enables clinicians to understand, at least in part, chronic musculoskeletal pain in CFS patients. Generalized joint hypermobility and benign joint hypermobility syndrome appear to be highly prevalent among CFS sufferers, but they do not seem to be of any clinical importance. On the other hand, pain catastrophizing accounts for a substantial portion of musculoskeletal pain and is a predictor of exercise performance in CFS patients. The evidence concerning pain catastrophizing is supportive of the indirect evidence of a dysfunctional pain processing system in CFS patients with musculoskeletal pain. CFS sufferers respond to incremental exercise with a lengthened and accentuated oxidative stress response, explaining muscle pain, postexertional malaise, and the decrease in pain threshold following graded exercise in CFS patients. Applying the scientific evidence to the manual physiotherapy profession, pacing self-management techniques and pain neurophysiology education are indicated for the treatment of musculoskeletal pain in CFS patients. Studies examining the effectiveness of these strategies for CFS patients are warranted.

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1. Introduction

The main feature of chronic fatigue syndrome (CFS) diagnosis is the exclusion of all conditions other than CFS (e.g. diabetes, cancer, and obesity), together with the presence of a debilitating fatigue lasting for at least 6 months (Holmes et al., 1988; Fukuda et al., 1994). Worsening of symptoms (pain, fatigue) is typically seen after previously well-tolerated levels of exercise/physical activity.

Chronic fatigue has been arbitrarily put forward as the primary symptom of CFS. Between 54% and 75%

of CFS patients experience chronic widespread pain (Nishikai et al., 2001). Chronic fatigue with widespread muscle and joint pain has been suggested as an important subclass of CFS (Tan et al., 2002), and the observed associations between musculoskeletal pain severity and disability (r between 0.51 and 0.58) was similar to the association between fatigue severity and disability ($r = 0.50$) (Nijs et al., 2003a, 2004a). The latter suggests musculoskeletal pain to be as important as fatigue to CFS patients.

A few years ago, little was known about the nature of chronic musculoskeletal pain in CFS. To date, scientific research data gathered around the world enables clinicians to understand, at least in part, chronic musculoskeletal pain in CFS patients. The present manuscript provides the reader with our current understanding of chronic musculoskeletal pain in CFS patients.

In the US, patients with CFS are often seen in chiropractic practise. Studying the health-care use of 402

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patients from a university-based chronic fatigue clinic, it was found that 27% of CFS patients visited chiropractors, and 12% visited osteopaths (Bombardier and Buchwald, 1996). Nearly 56% of the studied patients fulfilling the diagnostic criteria for both CFS and Fibromyalgia visited chiropractors, and 15.3% visited osteopaths. Although studies examining the effectiveness of interventions aiming at reducing musculoskeletal pain in CFS are scarce, the knowledge addressing chronic musculoskeletal pain in CFS enables clinicians to provide a plausible treatment strategy. Therefore, this manuscript provides suggestions for manual physiotherapists to treat chronic musculoskeletal pain in CFS patients.

2. Musculoskeletal pain in CFS: is generalized joint hypermobility an issue?

If generalized joint hypermobility appears to be an issue in CFS, then physiotherapists should include joint hypermobility in the assessment and management of CFS. Generalized joint hypermobility (assessed using the Beighton et al., 1973 criteria) was more prevalent in patients with CFS than in matched healthy controls (21% versus 4%; $P = 0.004$) (Nijs et al., 2006). The majority of CFS patients (58.8%) fulfilled the criteria for benign joint hypermobility syndrome (BJHS) (as described by Grahame et al., 2000). Knee proprioception was similar in both groups ($P = 0.81$), and no associations were found between generalized joint hypermobility and self-reported pain severity, disability, or knee proprioception. There appears to be no association between musculoskeletal pain and joint hypermobility in CFS patients (Nijs et al., 2004b). A review of the evidence on generalized joint hypermobility in Fibromyalgia and CFS, together with an overview on assessment and treatment strategies, is presented elsewhere (Nijs, 2005). If generalized joint hypermobility is not of clinical importance to CFS patients, then other factors must explain chronic musculoskeletal pain in CFS.

3. Musculoskeletal pain in CFS: a biopsychosocial explanation

The study showing decreased pain threshold following graded exercise in CFS patients (Whiteside et al., 2004) suggested a link between impaired exercise performance and pain experience in CFS patients (in healthy subjects, a substantial increase in pain threshold in response to exercise is typically observed). A recent study (Nijs et al., under review) provided evidence supportive of this assumption: pain catastrophizing was identified as a major predictor of exercise performance in female CFS

patients experiencing chronic widespread pain. In addition, pain catastrophizing was found to predict bodily pain, even after controlling for depression. From previous studies, it is concluded that fear of movement ('kinesiophobia') is not related to exercise performance in CFS patients (Nijs et al., 2004c,d). In addition, kinesiophobia in general (fear of an exercise-triggered increase in general symptom severity), rather than pain-related fear of movement, was related to self-reported disability in CFS patients (Nijs et al., 2004c).

There is a body of literature providing evidence for somatization (Johnson et al., 1996; Fischler et al., 1997) and activity-avoidance (Nijs et al., 2004c) in CFS patients. These cognitive styles and personality traits, together with pain catastrophizing, may result in sensitization of dorsal horn spinal cord neurons (through inhibition of descending tracks in the central nervous system), or are the result of central sensitization (Zusman, 2002). Central sensitization is defined as "an augmentation of responsiveness of central pain-signaling neurons to input from low-threshold mechanoreceptors" (Meyer et al., 1995). Direct evidence supporting the central sensitization hypothesis in CFS patients is currently lacking. Still, the observed decreased pain threshold following graded exercise in CFS patients is indicative of a dysfunctional central antinociceptive mechanism in CFS (Whiteside et al., 2004), and evidence of a deregulated serotonergic neurotransmission in the brain of CFS patients, consistent with altered pain processing, has been provided (Yamamoto et al., 2004). Strong evidence supportive of altered central sensory processing (i.e. central sensitization) among patients with Fibromyalgia has been published (Staud et al., 2001, 2003; Price et al., 2002; Banic et al., 2004). Studies examining whether these data apply to CFS patients with chronic widespread pain are underway.

The central sensitization hypothesis fits our current understanding of CFS psychopathology and pathophysiology. The link with CFS psychopathology has been outlined in the preceding paragraph. From a pathophysiologic perspective, the evidence of a high prevalence of opportunistic infections (e.g. Vojdani et al., 1998; Nijs et al., 2002) is consistent with the numerous reports of deregulated and suppressed immune functioning in CFS patients (e.g. Suhadolnik et al., 1997; Levine et al., 1998; Nijs et al., 2003b). Deregulation of intracellular immune function was even found to be a predictor of physiological exercise parameters (Nijs et al., 2005). Infection triggers the release of the pro-inflammatory cytokine interleukin- 1β , which is known to play a major role in inducing cyclooxygenase-2 (COX-2) and prostaglandin E2 expression in the central nervous system (Bazan, 2001; Samad et al., 2001). Upregulation of COX-2 and prostaglandin E2 sensitizes peripheral nerve terminals. Indeed, even peripheral infections activate spinal cord

glia (both microglia and astrocytes), which in turn enhance the pain response by releasing nitric oxide (NO) and proinflammatory cytokines (for a detailed description of these complex pathophysiological interactions, the interested readers are referred to [Maier and Watkins, 1998](#); [Watkins and Maier, 1999](#)). These dynamic immune-to-brain communication pathways can explain a wide variety of psychological and physiological symptoms (the ‘sickness response’) seen in patients with CFS.

In addition, [Vikman et al. \(2003\)](#) demonstrated that long-term treatment of cultured spinal dorsal horn neurons with interferon-gamma triggers NO-dependent reduction of GluR1 clustering on dendrites (GluR1 together with GluR2 are the two most prominent AMPA receptors in the superficial dorsal horn), accompanied by an enhanced spontaneous activity in the neuronal network. Since GluR1 is mainly associated with inhibitory neurons, these observations underscore the role of a NO-dependent reduction in inhibitory activity of the central nervous system in central sensitization. Since elevated NO levels have been documented in CFS patients ([Kurup and Kurup, 2003](#)), and oxidative stress was found to be associated with symptom expression (including musculoskeletal pain) in CFS patients ([Richards et al., 2000](#); [Vecchiet et al., 2003](#); [Kennedy et al., 2005](#)), the observations by [Vikman et al. \(2003\)](#) may explain part of the chronic pain experience in patients with CFS. Moreover, experimental evidence has shown that CFS patients respond to incremental exercise with a lengthened and accentuated oxidative stress response, explaining muscle pain and postexertional malaise as typically seen in CFS subjects ([Jammes et al., 2005](#)).

On the other hand, substance P levels do not seem to be upregulated in CFS patients ([Evengard et al., 1998](#)). Substance P, a peptide involved in the neurotransmission of pain from the periphery to the central nervous system, is typically elevated in patients with Fibromyalgia. Still, from the available evidence it is concluded that chronic widespread musculoskeletal pain in CFS patients fits our current understanding of the complex psychosocial interactions in CFS.

4. Manual physiotherapy as a treatment for chronic musculoskeletal pain in CFS patients?

What can the manual physiotherapy profession offer to patients with CFS experiencing chronic widespread musculoskeletal pain? From our current understanding of chronic musculoskeletal pain in CFS, as presented above, it is clear that hands-on manual therapy techniques are not indicated for treating chronic musculoskeletal pain in *all* CFS cases. Still, local musculoskeletal problems like thoracic outlet compres-

sion syndrome, low back pain, and neck pain are often seen in CFS patients. In selected cases, the local musculoskeletal problems may be more than epiphenomena: from our own clinic we recall patients reporting the onset of CFS symptoms after a Whiplash trauma, or after a rupture of the symphysis pubis during delivery and consequent lumbopelvic instability. In these patients, appropriate manual physiotherapy did *not cure the disease*, but was able to resolve the localized musculoskeletal pain problem and associated disability. Trained manual physiotherapists are able to differentiate between a localized and a central pain problem, even in a complex disorder like CFS. In case of the former, local manual therapy techniques are indicated, but should be adopted in respect to the reduced pain threshold and pathophysiology of the patient. In case of the latter, behavioural treatment strategies and pain neurophysiology education are indicated. This will be explained in the next paragraphs.

What kind of behavioural treatment can diminish musculoskeletal pain in CFS patients? The effectiveness of graded exercise therapy and cognitive behavioural therapy for CFS patients has frequently been examined. In many of the published studies, graded exercise therapy has been adopted as a component of the cognitive behavioural programme (i.e. graded exercise was used as a way to diminish avoidance behaviour towards physical activity). According to the Cochrane Library, both treatment strategies are effective in the short term for treating CFS patients ([Price and Couper, 1998](#); [Edmonds et al., 2004](#)). Unfortunately, the studies examining the effectiveness of graded exercise therapy/cognitive behavioural therapy in CFS did not use (musculoskeletal) pain as an outcome measure (e.g. [Deale et al., 1997](#); [Fulcher and White, 1997](#); [Powell et al., 2001](#); [Prins et al., 2001](#)). Secondly, none of the studies referenced here applied the current diagnostic criteria for CFS ([Fukuda et al., 1994](#)), making it difficult to extrapolate these results to other settings. Thirdly, from a large treatment audit among British CFS patients, it was concluded that approximately 50% of the patients stated that graded exercise therapy worsened their condition ([Shephard, 2001](#)). Finally, graded exercise therapy does not comply with our current understanding of CFS exercise physiology. As outlined above, experimental evidence is now available showing increased oxidative stress in response to (sub)maximal exercise and subsequent increased fatigue and musculoskeletal pain (postexertional malaise).

Pacing, a strategy where patients are encouraged to achieve an appropriate balance between activity and rest in order to avoid exacerbation and to set realistic goals for increasing activity, is an alternative for the cognitive behavioural approach (CFS/ME Working Group, 2001; [Shephard, 2001](#)). This energy management strategy involves avoiding activities to a degree that exacerbates

symptoms or interspersing activity with periods of rest (CFS/ME Working Group, 2001; Shephard, 2001). Contrary to the cognitive behavioural approach, pacing takes into account the considerable fluctuations in symptom severity (Shephard, 2001) and the delayed recovery from exercise (Paul et al., 1999) that typically occurs in patients with CFS. The pacing approach is consistent with the recent observations regarding the interactions between malfunctioning of the immune system, physical activity, and musculoskeletal pain in CFS patients. The first goal of the pacing approach is to enable the CFS patient to manage his/her daily activities in a way he/she no longer experiences fluctuations in symptoms (stabilization phase). Next, the physiotherapist can start to grade activity and exercise levels (grading phase). During the grading phase, the same pacing techniques are applied to grade both activity level and exercise level (i.e. flexible, accounting for the fluctuating nature of the disorder). To prevent overactive patients in exceeding their own limits, heart rate monitoring can be applied for intensity control (heart rate guidelines are obtained from the exercise stress test with continuous cardiorespiratory monitoring). This type of graded exercise has been found to be superior over relaxation and flexibility training in CFS patients (Wallmann et al., 2004).

Finally, pain neurophysiology education might be indicated for CFS patients with musculoskeletal pain. As outlined above, pain processing is likely to be abnormal in CFS patients, and evidence showing that pain catastrophizing accounts for a substantial portion of musculoskeletal pain in CFS has been provided. Pain neurophysiology education was found to be effective in reducing pain catastrophizing in chronic low back pain patients (Moseley, 2002; Moseley et al., 2004).

5. Conclusion

Recent studies have provided new insights into our understanding of chronic widespread musculoskeletal pain in CFS patients. Generalized joint hypermobility and BJHS appear to be highly prevalent among CFS sufferers, but they do not seem to be of any clinical importance. On the other hand, pain catastrophizing accounts for a substantial portion of musculoskeletal pain and exercise performance in CFS patients. The evidence concerning pain catastrophizing is supportive of the indirect evidence of a dysfunctional pain processing system in CFS patients with musculoskeletal pain. CFS sufferers respond to incremental exercise with a lengthened and accentuated oxidative stress response, explaining muscle pain, postexertional malaise, and the decrease in pain threshold following graded exercise in CFS patients. Applying the scientific evidence on musculoskeletal pain to the practise of manual phy-

siotherapy, pacing self-management techniques, and pain neurophysiology education are indicated for the treatment of musculoskeletal pain in CFS patients. Studies examining the effectiveness of these strategies for CFS patients are warranted.

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