Pathogenesis, Diagnosis and Treatment of Fibromyalgia: An Update

Anselm Mak and Edmund K Li

Abstract: Fibromyalgia is not an uncommon condition. Although the American College of Rheumatology (ACR) has devised a set of criteria to classify fibromyalgia, whether it really exists as a distinct disease entity is still under continuing debate. Undoubtedly, fibromyalgia carries significant morbidity and socioeconomic impact to societies. Effective management with the aim of normalisation of daily activities is the main goal of management. In this article, the diagnosis and treatment of fibromyalgia are briefly discussed.

Keywords: Ache and pain, fibromyalgia, prognosis

Introduction

The American College of Rheumatology (ACR) devised a set of diagnostic criteria for the classification of fibromyalgia in 1990. Fibromyalgia is classified if one has chronic widespread pain (CWP) for more than three months with affected pain threshold as evidenced by increased tenderness at any eleven out of the eighteen specified tender points (Figure 1). CWP represents generalised pain distributed over both sides of the body, both above and below the waist. Involvement of pain over the axial skeleton is mandatory.

The local prevalence of fibromyalgia is still unclear. Population-based series in western countries showed that the prevalence of fibromyalgia ranged from 0.7% to 3.3%, with a female preponderance. An incidence of 0.6% was reported in a Norwegian survey in women aged 20 to 49 years. By intuition, fibromyalgia is not a fatal disease. A recent prospective study of over 8-year duration however demonstrated a standard mortality rate of 1.31 in people with CWP. The main cause of death in this group of people was malignancy and smoking was one of the most important risk factors for death. Besides the negative impact on individual patients, impact of fibromyalgia on societies is also tremendous. A survey in the US revealed that chronic musculoskeletal condition constituted 2.5% of the Gross National Product (GNP) in early 1990s. Further elucidation of the disease mechanism and effective management of fibromyalgia is therefore prudent in order to improve the prognosis and alleviate its negative impact on societies.

Does Fibromyalgia Exist as a Distinct Disease Entity?

The ACR criteria are primarily to define fibromyalgia and aid clinical research into this heterogeneous condition which have previously been poorly defined. Despite, it arouses hot
discussions on whether it is a real disease entity in the epidemiological and clinical perspectives. Epidemiologically, the lack of definite and clear clinical features, risk, protective or prognostic factor and specific treatment response render fibromyalgia indistinct to be a single disease entity.12-14

Practically, physicians are faced with patients who present with symptoms of fibromyalgia. In physicians' perspective, diagnosing a patient with fibromyalgia can guide further management instead of lingering on mixtures of non-specific symptoms without a specific direction. Recruitment of suitable subjects for clinical studies of fibromyalgia is facilitated with the presence of classification criteria. However, fibromyalgia patients may be labelled demanding and anxious and it would ruin the doctor-patient relationship, an essential component for successful management. In patients' perspective, ability of arriving at a diagnosis builds confidence towards the physicians and treatment plan. Good patient-doctor relationship and subsequent compliance are enhanced. On the contrary, sick role of fibromyalgia may be adopted inappropriately.

In short, whether fibromyalgia is a distinct disease warrants further epidemiological and clinical studies. However, the controversy should not deter physicians from making the correct diagnosis of fibromyalgia so that appropriate management can be given.

**Aetiology and Trigger Factors**

The aetiology and pathogenesis of fibromyalgia remains unclear. Several possible mechanisms have been proposed. Of these, the neurobiochemical and psycho-behavioural mechanisms have been widely studied. Environmental triggering factors which promote fibromyalgia development in susceptible individuals have also been described. Altered central pain processing with central nociceptive hyperexcitability coupled with decreased pain inhibitory neural signals descending from the brainstem was postulated to generate the widespread pain syndrome and tender spots in fibromyalgia patients.15,16 In agreement with previous clinical experiments, a recent study further demonstrated that nociceptive thresholds to temperature and pain were significantly lower in patients with fibromyalgia compared with healthy controls.17 Using functional magnetic resonance imaging, it was shown that less pressure stimuli were required to trigger cerebral activation in the somatosensory cortices in fibromyalgia patients compared with healthy controls.18 One of the important symptoms of fibromyalgia is sleep disturbance. Insomnia is a frequent complaint of fibromyalgia patients and abnormalities in sleep electroencephalograph (EEG) are commonly found. Up to 80% of fibromyalgia patients show a characteristic pattern of abnormality with a wave intrusion into the normal d rhythm of non-REM (stage 4) sleep. Although not specific to fibromyalgia, this irregular sleep pattern may be an important factor contributing to the severity of symptoms. Muscle symptoms have been shown to develop in healthy subjects with experimentally disturbed sleep and it may be related to serotonin deficiency in this subset of patients.19

Biochemical studies revealed higher concentrations of substance P in the cerebrospinal fluid (CSF) of fibromyalgia patients20 as in other chronic pain syndromes. Dysregulated vasoconstrictory response could be partially explained by abnormally high level of substance P in the CSF causing Raynaud’s-like phenomenon in subsets of fibromyalgia patients.21 Lower CSF concentration of norepinephrine, which is an important neurotransmitter to mediate the descending pain-inhibitory neural pathways, was demonstrated in fibromyalgia patients.22 Serotonin (5-HT) has a central role in the regulation of sleep, pain and mood.23 Reduced levels of serum and CSF 5-HT and its metabolites in some fibromyalgia patients suggested that defective synthesis or metabolism of 5-HT may be a possible mechanism of the condition. Finally, serum insulin-like growth factor-1 (IGF-1) was demonstrated to be lower in fibromyalgia patients.24

Psycho-behavioural mechanisms have also been postulated to play an important role in symptom manifestations in fibromyalgia. Since a considerable overlap between major affective disorders and fibromyalgia is present, some authorities postulated that fibromyalgia is a part of the affective spectrum disorders.25 Controlled studies demonstrated that anxiety and depressive disorders occurred up to 60% of fibromyalgia patients. Lifetime risks for development of psychiatric disorders were also higher compared to healthy controls.26 Nevertheless, the concept that fibromyalgia is a somatoform disorder of psychiatric conditions is obsolete. Depression is suggested not to be a causative factor of fibromyalgia.27 Though there is a strong suggestion that fibromyalgia patients experience considerable psychological distress, this may simply be a manifestation of frustration resulting from long-standing unrelenting pain and fatigue.28
Environmental factors may be important in triggering the development of fibromyalgia. Certain infective triggers including infections with parvovirus, Epstein-Barr virus, Q-fever and leptospira burgdorferi (Lyme disease) were reported. History of physical trauma particularly skeletal injury as a triggering factor was also reported. Catastrophic events such as war, natural and manmade disasters were extensively described to be possible triggers in the development of fibromyalgia.29

Clinical Features

Fibromyalgia is not solely the combination of CWP and tender points. A pattern of specific complaints and presentation is usually observed in fibromyalgia patients. All patients with fibromyalgia complain of chronic, severe and disabling pain associated with generalised tenderness without a specific reason. Ninety-six percent to all of the fibromyalgia patients present with fatigue associated with depression. The common phenomena of fatigue include "physical weakness", "loss of energy" or "loss of interest". Eighty-six percent to 98% percent of them complain of sleep disturbance. Sleep is characteristically non-refreshing and patients usually get up in the morning with generalised pain and tenderness.30

Fibromyalgia patients also exhibit various co-morbidities as listed in Table 1.31 Of particular interest is chronic fatigue syndrome (CFS). The US Centres for Disease Control and Prevention (CDC) has developed diagnostic criteria for CFS (Table 1). The overall prevalence of CFS is estimated at 1% of the general population with approximately 70% of those affected being women.32 CFS and fibromyalgia share similar symptomatology. Both are associated with fatigue, sleep disturbance, musculoskeletal pain and psychiatric conditions. However, patients with CFS are more likely to have symptoms suggestive of viral infection including low grade fever, sore throat and tender lymph glands. CFS usually presents with a sudden onset of symptoms which sufferers are usually able to recall. In addition, patients with CFS may have impaired concentration and memory. Though many patients with CFS have tender points, their presence is not necessary for diagnosis.33 Clinical presentation of fibromyalgia is therefore diverse and complex. Careful and tactful analysis of patients' symptoms with recognition of the presentation pattern is a crucial step towards making the correct diagnosis.

Conditions Mimicking Fibromyalgia

Many conditions share similar symptomatology with fibromyalgia (Table 2).34 Careful history taking, tactful clinical examination and appropriate laboratory tests can help figuring out the disease condition. It is worth noting that those conditions listed could co-exist with fibromyalgia and the term "secondary fibromyalgia" is adopted by some rheumatologists. Undoubtedly, proper treatment of the underlying conditions is the most important.

Investigations

Fibromyalgia is a clinical diagnosis. No single test can help confirm the diagnosis. Blood tests are sometimes required to exclude potentially reversible and even serious conditions. Investigations should be guided by history, clinical symptoms and signs suggestive of those conditions listed in Table 2. Complete blood picture, screening for diabetes mellitus, liver and renal function tests including alkaline phosphatase and calcium levels form the basic screening tests during initial visits. Clearly, an abnormal screening test warrants further investigations. Thyroid function tests, serum muscle enzyme levels, autoimmune markers, erythrocyte sedimentation rate

Table 1. Various co-morbidities in fibromyalgia syndromes and their point prevalences

<table>
<thead>
<tr>
<th>Co-morbid syndrome</th>
<th>Point prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic low back pain</td>
<td>67</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>59</td>
</tr>
<tr>
<td>Mood disorder</td>
<td>29</td>
</tr>
<tr>
<td>Temporomandibular joint disorder</td>
<td>24</td>
</tr>
<tr>
<td>Chronic tension headache</td>
<td>23</td>
</tr>
<tr>
<td>Chronic fatigue syndrome (CFS) +</td>
<td>18</td>
</tr>
<tr>
<td>Multiple chemical sensitivities (MCS) ++</td>
<td>18</td>
</tr>
<tr>
<td>Chronic pelvic pain</td>
<td>18</td>
</tr>
<tr>
<td>Interstitial cystitis +++</td>
<td>8</td>
</tr>
</tbody>
</table>

+: CFS is characterised by severe fatigue plus 4 out of 8 of the followings: myalgia, arthralgia, sore throat, tender neck, cognitive difficulty, headache, post-exertional malaise and/or sleep disturbance

++: MCS is characterised by sensitivity to numerous environmental exposures, with resultant unexplained symptoms in multiple organ systems

+++: Interstitial cystitis is also known as female urethral syndrome characterised by chronic irritative voiding symptoms with sterile urine
and C-reactive protein levels substantiate clinical suspicions of hypothyroidism, myositis and other rheumatological conditions respectively.

It is important not to over-investigate fibromyalgia patients since it may just exacerbates sick role behaviour without gaining circumferential evidence for making the clinical diagnosis.

**Pharmacological Management**

Different classes of drugs for the treatment of fibromyalgia have been studied extensively and many of them demonstrated promising results in randomised controlled trials. A list of drugs commonly used in managing fibromyalgia is shown in Table 3. Of particular mention are tricyclic antidepressant (TCA), selective serotonin reuptake inhibitors (SSRIs), non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, benzodiazepines and opiates.

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Pharmacodynamics</th>
<th>Pain</th>
<th>Sleep</th>
<th>Fatigue</th>
<th>Mood</th>
<th>Other FSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA</td>
<td>Amitriptyline</td>
<td>5HT/NE re-uptake blockade, NMDA blockade, AH/AC</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>IBS, TMJD, LBP, CTTH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NMDA blockade, AH/AC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>prophylaxis</td>
</tr>
<tr>
<td>SSRI</td>
<td>Fluoxetine</td>
<td>5-HT reuptake blockade</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>CTTH prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Citalopram</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRI</td>
<td>Venlafaxine</td>
<td>5HT&gt;NE reuptake blockade</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>CTTH prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Milnacipran</td>
<td>NE&gt;5HT reuptake blockade</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>MAOI</td>
<td>Moclubemide</td>
<td>MAO-A inhibitor</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>CTTH prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Pirlindole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CFS</td>
</tr>
<tr>
<td>NRI</td>
<td>Reboxetine</td>
<td>NE reuptake blocker</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Ibuprofen</td>
<td>COX inhibitor</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>LBP</td>
</tr>
<tr>
<td>AED</td>
<td>Pregabalin</td>
<td>Ca++ channel blocker</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedative-hypnotics</td>
<td>Zopiclone</td>
<td>BZ receptor agonist</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle relaxants</td>
<td>Cyclobenaprine</td>
<td>5HT2 antagonist</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td></td>
<td>CTTH, IBS</td>
</tr>
<tr>
<td></td>
<td>Tizanidine</td>
<td>AC/AH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LBP</td>
</tr>
<tr>
<td>Opiates</td>
<td>Tramadol</td>
<td>µ agonist</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>CTTH LBP</td>
</tr>
</tbody>
</table>

A: -, no benefit; +, beneficial; blank not tested in trials

B: TCA, tricyclic antidepressants; NMDA, N-methyl-D-aspartate; AH, antihistaminergic; AC, anticholinergic; IBS, irritable bowel syndrome; TMJD, temporomandibular joint disease; CTTH, chronic tension-type headache; CFS, chronic fatigue syndrome; LBP, low back pain; SSRI, selective serotonin reuptake inhibitor; DRI, dual reuptake inhibitor; HT, serotonin; NE, norepinephrine; FSS, functional somatic syndromes; MAOI, monoamine oxidase inhibitor; NRI, norepinephrine reuptake inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; AED, antiepileptic drugs; BZ, benzodiazepine
The TCA, amitriptyline, has been widely used in the treatment of fibromyalgia. It has been shown to be efficacious by numerous randomised controlled trials except in the improvement of mood.36 Being used as small doses explains its poor efficacy in mood improvement. Amitriptyline should be started at 10 mg orally one to two hours before sleep and may be stepped up to 50 mg daily. Clinical improvement should been seen within 3 months of treatment. Review of diagnosis of fibromyalgia or switching to other classes of drugs should be considered if amitriptyline is found to be inefficacious. Anticholinergic or antihistamineergic side-effects give rise to poor side-effect profile of TCA. Patients with concomitant multiple chemical sensitivities (Table 1) may be particularly vulnerable to the side effects of TCA.

SSRIs exhibit a better side-effect profile than TCA as anticholinergic and antihistamineergic effects are absent. They are usually considered if patients cannot tolerate or are contraindicated to TCA. Fibromyalgia patients with concomitant mood symptoms would be particularly benefited from SSRIs as evidenced by its superior efficacy towards mood symptoms in randomised controlled trials.37

Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol have been widely used in fibromyalgia patients.38 However, a large number of controlled trials failed to demonstrate their efficacy towards enhanced analgesia in fibromyalgia patients. Nevertheless, there is limited evidence demonstrating their benefit in pain improvement in fibromyalgia patients co-morbid with osteoarthritis, rheumatoid arthritis and lupus.39 This evidence further reflects that the mechanism of pain generation in fibromyalgia is not originated at the level of noxious peripheral pain receptor stimulation.

The use of corticosteroids in the treatment of fibromyalgia was tested in a double-blind, placebo-controlled cross-over trial. Patients assigned to take prednisolone 15 mg daily demonstrated no significant difference in pain, sleep, fatigue and dolorimeter scores compared with those taking placebo.40

Benzodiazepines are efficacious in improving sleep and fatigue but not pain in fibromyalgia patients. Its early use as bridging therapy to alleviate anxiety symptoms while awaiting the full therapeutic effects of TCA was promising.41

Opiates were also widely used in fibromyalgia patients. In the US, about 14% of patients receive opiates.38 Tramadol is the widely used and studied opiate in fibromyalgia. Two randomised controlled trials demonstrated its promising efficacy in pain improvement. It was recommended to start at 50 mg twice daily and escalate to a maximum dose of 100 mg four times daily. An increased seizure risk was reported when the dose exceeds the maximum.42,43 In addition, dependence, negative effect on cognition, stigmatisation and reduced motivation to pursue non-pharmacological intervention are drawbacks of opiate treatment.

Less commonly used drugs not shown in Table 2 are 5HT-3 antagonists (Tropisetron), NMDA receptor antagonists and growth hormone (GH). Of particular interest is GH. A randomised, double-blind controlled trial of 50 premenopausal fibromyalgia women with predetermined low IGF-1 level showed a significant improvement in FIQ (Fibromyalgia Impact Questionnaire) scores and tender-point counts in 9 months compared with the placebo group.44 However, the high cost and paucity of long term efficacy data of GH preclude its widespread application in fibromyalgia patients.

Non-pharmacological Management

Pharmacological approach alone benefits less than fifty percent of patients and only twelve percent of them can ultimately achieve long lasting functional status improvement.45,46 Of various non-pharmacological management modalities being investigated, exercise and cognitive-behavioural therapy have been extensively studied. Overall there have been about thirty randomised controlled trials conducted to investigate the benefit of exercise (and types of exercise) in fibromyalgia patients. Though the results of the trials were heterogeneous, a meta-analysis showed that moderate intensity exercise including walking, cycling and pool exercise can improve symptoms and functional status of fibromyalgia patients. An exercise frequency of twice weekly is sufficient to improve aerobic capacity and reduce tenderness for fibromyalgia patients. Post-exertional pain is important and should be specifically sought since it could affect patients' compliance of exercise programmes. One of these largest trials involving 120 fibromyalgia subjects showed a 50% non-compliance rate of exercise mainly secondary to post-exertional pain.47 Exercise prescription should therefore be individualised and based on individual patient's baseline function, severity of pain, fatigue and tolerance. Occurrence of post-exertional pain warrants
modification of exercise programme to a less vigorous one. Cognitive-behavioural therapy (CBT) is originated from psychological and behavioural therapies in managing anxiety disorders, depression and chronic pain. It comprises a set of psychotherapeutic skills aiming at modifying behaviour based on the classical and operant conditioning and observation learning. Skills including education, pain coping, pleasant activity scheduling, assertive training, relaxation, sleep hygiene, relapse prevention, etc. are introduced during CBT sessions for fibromyalgia patients. The favourable outcome of CBT is to achieve a positive development of effective problem-solving skills. Managing fibromyalgia with CBT alone produces only modest decrease in pain as shown by two uncontrolled studies.48,49 A recent controlled study demonstrated that an addition of six one-hour sessions of CBT to existing pharmacological and exercise management in fibromyalgia patients produced significant improvement in functional status.46 Despite the encouraging results, provision of CBT is often restricted by the paucity of psychotherapists in our local clinical settings.

**Prognosis**

The inclusion of chronic widespread pain in the diagnostic criteria signifies fibromyalgia should have a long natural course. In a multi-center longitudinal study, the median duration at presentation is over 7 years and the course over a long follow-up is unremitting.50 However, reports regarding high rates of improvement of fibromyalgia symptoms over time and variability of symptom severity between subjects in general populations and rheumatology clinics suggest the natural course is variable and to be speculative.6

**Treatment Strategy**

Reassurance is essential in fibromyalgia patients. Concepts of absence of tissue damage and availability of various effective treatment modalities may alleviate anxiety of fibromyalgia patients. Medications should be tailored to individual patients targeting at specific symptoms and comorbidities. Adequate explanation on their efficacies and potential adverse effects is crucial to achieve better compliance. Exercise programmes stressed on adequate warm-ups should be prescribed but need to be individualised. Advice from physiotherapists is an advantage. Post-exercise pain should be specifically enquired during subsequent clinical encounters. Healthy sleep hygiene is stressed. Availability of clinical psychologists is essential for prescribing cognitive-behavioural therapy. Efficacy of combination of pharmacological therapy with exercise and cognitive-behavioural therapy seems encouraging. Leaflets can consolidate information conveyed to patients. Patients should be encouraged to join self-help groups and participate in social activities in order to strengthen their coping skills and achieve a state of control over the distressing symptoms, which is the ultimate goal of management of fibromyalgia.

**Conclusion**

Though the aetiology and pathogenic mechanisms of fibromyalgia remain elusive, the complex interplay between neurobiochemical, psycho-behavioural and environmental factors may contribute. More experiments and clinical studies are required to shed more insights into the condition. Without scepticism, a proper management strategy aiming at normalisation of daily living of fibromyalgia patients is prudent to alleviate its negative impacts towards health care systems and societies.

**References**

FIBROMYALGIA UPDATE


