How to diagnose fibromyalgia

This review discusses the basic pathophysiological mechanisms that are necessary to understand the principles of diagnosis and management of fibromyalgia, and outlines a practical diagnostic approach to patients presenting with chronic widespread pain.

Chronic widespread pain is a common problem, with an estimated prevalence of between 4.7% and 11.2% in various populations (Croft et al, 1993; Hunt et al, 1999). An underlying medical condition is likely to account for widespread pain in only a small proportion of patients (Reilly, 1999a). In a vast majority, the pain cannot be explained on the basis of a disease model because of the absence of objective physical signs (apart from tender points and pain amplification), and normal (or irrelevant) imaging or laboratory test results. Patients with chronic unexplained widespread pain often suffer with numerous other unexplained symptoms such as fatigue, headaches, jaw pain, chest pain, paraesthesias, altered bowel habits, urinary urgency and pelvic pain, and are therefore likely to be encountered by doctors across multiple specialties. Terms like 'somatisation', 'functional somatic syndromes' or 'medically unexplained symptoms' have been used to describe such symptoms that cannot be explained on a medical basis (Hatcher and Arroll, 2008).

Medical practitioners are generally comfortable dealing with patients whose symptoms can be explained by organic pathology. Those who present with unexplained subjective symptoms are usually perceived to be difficult, and labelled as 'heart sink patients'. Such patients are often made to feel that the problem 'could be in their head'. Nevertheless, medically unexplained symptoms can cause as much disability as symptoms caused by organic disease (Carson et al, 2000). Also, costs of managing patients with unexplained symptoms are tremendous because of repeated and unnecessary investigations, referrals to various specialists, inappropriate treatments, loss of productivity, and social security payments (Skaer, 2014).

This review focuses on those patients who present with 'medically unexplained' chronic widespread pain that is labelled as fibromyalgia. An overview of pathogenesis is presented, followed by an outline of the principles of diagnosis.

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Pathogenesis of fibromyalgia

Pathogenesis of fibromyalgia is complex and multi-factorial, so only the basic details necessary to understand the principles of diagnosis and management are presented. The exact sequence of events that culminates in the development of this syndrome remains elusive, but it is probably triggered by a combination of genetic and environmental factors.

Central pain sensitization

When peripheral pain receptors (nociceptors) are stimulated by tissue injury or inflammation, afferent sensory impulses are transmitted through first order peripheral neurones to the dorsal horn of the spinal cord (Besson, 1999). This sensory input is then transmitted along central pain pathways (spinothalamic tract) to the thalamus, and then from the thalamus to the cerebral cortex resulting in the perception of pain sensation. The sensory input from the thalamus is also relayed to the limbic system, where the emotional aspect of pain is processed.

The afferent sensory impulses from first order peripheral neurones stimulate the release of substance P, excitatory neurotransmitters such as glutamate and nerve growth factor, and inflammatory cytokines such as prostaglandins and nitric oxide. These mediators open up the N-methyl-D-aspartate (NMDA) channels in the dorsal horn to facilitate transmission of sensory impulses through the central pain pathways. There are also other pathways that descend from the higher centres ('descending pain pathways') involving neurotransmitters such as serotonin and noradrenaline, which have the opposite effect, exerting an inhibitory influence on the dorsal horns. These descending pathways prevent unwanted signals from reaching the nervous system.

Patients with injury or inflammation (e.g. appendicitis, fracture or synovitis) experience pain because of nociceptor stimulation, and their pain would be expected to be proportional to the amount of tissue injury or inflammation. Treating the underlying problem that stimulates nociceptors (e.g. appendectomy, fracture reduction or intra-articular corticosteroids) would therefore be expected to abolish pain in such patients. Patients with fibromyalgia, on the other hand, experience pain because of central pain sensitization, which means that the periph-

eral sensory input is augmented in central pain pathways through complex mechanisms. Instead of serving a protective function, the pain becomes the 'disease' in these patients.

There are several indirect lines of evidence in favour of the theory of central pain sensitization:

- CSF levels of substance P and nerve growth factor, and brain levels of glutamate are higher in patients with fibromyalgia than in healthy controls (Russell et al, 1994; Giovengo et al, 1999; Valdes et al, 2010)
- Some small studies, but not all, have demonstrated lower plasma levels of serotonin, and lower CSF levels of serotonin and noradrenaline metabolites among fibromyalgia patients (Russell et al, 1992a,b)
- The NMDA receptor antagonists, ketamine and dextromethorphan, attenuate pain in patients with fibromyalgia (Graven-Nielsen et al, 2000; Staud et al, 2005)
- Functional magnetic resonance imaging studies have demonstrated that when stimuli of equal intensity are applied, patients with fibromyalgia have increased activity in those parts of the brain that code for sensory intensity of stimuli, compared to healthy controls (Gracely et al, 2002)
- There is no convincing evidence for pathology in the muscle, or altered muscle metabolism among patients with fibromyalgia when compared to controls (Bengtsson et al, 1986; Simms et al, 1994).

Thus patients with fibromyalgia experience pain in the absence of tissue inflammation (or pain that is out of proportion to the injury or inflammation), hyperalgesia (pain amplification) and allodynia (light stimuli perceived as painful). There is also augmentation of olfactory and auditory stimuli, and reduced threshold to heat, cold and electrical stimuli, suggesting general hypervigilance (Rodrigues et al, 2005). Interestingly, similar findings of hyperalgesia and allodynia have been noted in patients with tension headache, temporomandibular joint dysfunction, irritable bowel syndrome, interstitial cystitis and vulvodynia as well (Langemark et al, 1989; Maixner et al, 1995; Ness et al, 2005; Hampson et al, 2013), thus providing a common link between these different functional somatic symptoms.

These mechanisms explain why analgesics or anti-inflammatories that target peripheral nociceptors are unhelpful for patients with fibromyalgia, while drugs that limit the release of glutamate such as pregabalin, and those that increase the levels of serotonin and noradrenaline such as duloxetine, are helpful.

Non-restorative sleep

Almost all fibromyalgia patients complain of feeling unrefreshed on waking in the mornings and complain of daytime tiredness because of fragmentation of deep sleep (Davies et al, 2008; Choy, 2015). Even those patients who deny any sleep disturbance admit to feeling tired on waking in the mornings, indicating poor sleep quality.

In one study of selective sleep deprivation conducted among 13 healthy volunteers, deep sleep was deprived in six subjects, and rapid eye movement sleep in the remainder (Moldofsky and Scarisbrick, 1976). Muscle pains, mood disturbance and muscle tenderness developed more commonly among those in whom deep sleep was fragmented, and all symptoms completely resolved following restoration of deep sleep.

It has been suggested that musculoskeletal pains are induced by deprivation of deep sleep because growth hormone is mainly secreted during the deep sleep phase. Growth hormone is the precursor of insulin-like growth factor (IGF-1) which plays an important role in maintaining muscle homeostasis and repairing muscle microtrauma that develops during daytime activity. Serum levels of IGF-1 are significantly lower among patients with fibromyalgia (Bennett et al, 1992), and therapy with recombinant growth hormone is helpful (Bennett et al, 1998). Drugs that improve deep sleep are therefore helpful to not only improve sleep quality and tiredness, but also to reduce pain among patients with fibromyalgia.

Hypothalamic–pituitary–adrenal axis and autonomic dysfunction

During health, the stress response system is important to maintain homeostasis. Two important components of the stress response system interact closely with one another: the autonomic nervous system and the hypothalamic–pituitary–adrenal axis.

There is evidence for autonomic nervous system dysfunction among patients with fibromyalgia, with resultant hyperadrenergic tone (Martinez-Lavin and Hermosillo, 2000). It has been suggested that this hyperadrenergic tone may lead to a chronic stress state, resulting in different 'functional somatic' manifestations such as muscular discomfort because of increased muscular tension, sleep disturbance, fatigue, cognitive dysfunction (possibly as a result of cerebral vasoconstriction), disturbed bowel and bladder function, sexual dysfunction, cold hands and sicca symptoms. In some patients, increased adrenergic tone could be explained on the basis of genetic polymorphisms of the enzyme catechol-O-methyltransferase that helps to break down catecholamines such as adrenaline and noradrenaline (Ablin and Buskila, 2015).

Dysfunction of the hypothalamic–pituitary–adrenal axis has also been demonstrated among patients with fibromyalgia, with elevated levels of cortisol and lack of typical diurnal variation (Griep et al, 1993; Crofford et al, 1994). Patients also exhibit blunted cortisol response to administration of corticotrophin-releasing hormone, possibly because of the background hypercortisolaemia that leads to blunted adrenocorticotrophic hormone response or persistent background secretion of corticotrophin-releasing hormone that leads to downregulation of corticotrophin-releasing hormone receptors in the

anterior pituitary gland. Interestingly, similar dysfunction of the hypothalamic–pituitary–adrenal axis has been consistently noted among patients with major depression, and in those with a history of childhood sexual abuse (but without fibromyalgia)(Heim et al, 2000).

It is not known if the hypothalamic–pituitary–adrenal axis perturbations are the cause or consequence of fibromyalgia (Crofford, 2002). Whatever the underlying mechanism, patients exhibit reduced responsiveness to stress because of hypothalamic–pituitary–adrenal axis dysfunction, and possibly become unable to cope with the usual psychosocial stressors. Onset of fibromyalgia could therefore be triggered by stress states such as viral illnesses, physical trauma, or diagnosis of a chronic illness such as rheumatoid arthritis or systemic lupus erythematosus. It has been suggested that the blunting of stress axis response may result from repeated and inappropriate stimulation of the stress axis by previous traumatic life events, sometimes beginning during childhood.

Unhelpful thoughts, emotions and behaviours

Lastly, it is important to note that perception of pain sensation cannot be explained on the basis of anatomical and physiological mechanisms alone. Just as in any other illness, there are psychological and social aspects as well. Unhelpful thoughts, emotions (such as anxiety, depression and fear) and behaviours (such as avoidance, reduction in physical activity) contribute to aggravating the problem. The reduction in physical activity as a result of pain and tiredness may lead to physical deconditioning and reduced fitness, thus aggravating the sleep disturbance and setting up a vicious cycle.

Patients with fibromyalgia have increased rates of psychiatric comorbidity such as depression, anxiety, post-traumatic stress disorder and somatisation (Weir et al, 2006), and these conditions may predispose to the development of fibromyalgia, or its maintenance. One World Health Organization survey of primary care practices around the world reported that 22% of patients who reported persistent pain were four times more likely to suffer with depression or anxiety (Gureje et al, 1998). One Canadian study found that depression was three times more likely among patients with fibromyalgia than in the general population (Fuller-Thomson et al, 2012). Also, the presence of tender points (see below) is strongly associated with psychological distress (McBeth et al, 1999).

It was previously not clear if the psychiatric comorbidity was the cause or consequence of fibromyalgia, but the results of one large population-based prospective study indicated that the presence of the constellation of symptoms that suggest somatisation can predict the onset of chronic widespread pain (McBeth et al, 2001). The bottom line is that the treating physician should not forever keep hunting for an underlying organic cause when faced with a patient with chronic widespread pain, and bear in mind that treatment should involve a multidisciplinary approach, focussing on not only reducing pain (by using drugs that reduce central sensitization rather than the ones that target peripheral nociceptors), but also the associated sleep disturbance, physical deconditioning and psychological distress.

Controversies with diagnostic labelling

Whether or not to apply the fibromyalgia label for patients with chronic widespread pain has been a matter of debate (Ehrlich, 2003; Hadler, 2003; Goldenberg, 2004). Because this label is offered for patients with only subjective symptoms, there has been criticism that this concept could be exploited by those who seek personal gains such as workers' compensation, personal injury payouts and early retirement pensions. Critics argue that the concept of fibromyalgia may provide an official medical stamp of approval for those who fail to cope with occupational or domestic stress. However, in the UK, work absence as a result of back pain and invalidity payments accelerated exponentially only after the label was changed from 'spinal osteoarthritis' to 'simple back pain' during the 1980s (Reilly, 1999b).

There are several other arguments in favour of offering a diagnostic label. Because patients often feel frustrated that they have to 'prove their illness', it would give them a great sense of relief to know that their symptoms have been acknowledged as real. One study of patients with chronic fatigue syndrome reported that over 90% felt that getting a diagnosis was the single most helpful event during the course of their illness (Clements et al, 1997). It helped them to get closure, move forward, equip themselves with further knowledge through internet or books, or perhaps join patient support groups. It also helps the doctor to stop looking for the unknown, ordering unnecessary investigations or making further referrals. Importantly, offering a diagnostic label does not have a negative influence on the clinical outcome of patients with fibromyalgia, or lead to increased use of health service resources (White et al, 2002; Hughes et al, 2006). The reduction in costs following the diagnosis was attributed to a reduction in laboratory or imaging tests, GP visits, specialist referrals and unnecessary interventions.

Which patients with chronic widespread pain can be diagnosed with fibromyalgia?

The differential diagnosis for widespread pain is wide (*Table 1*) (Reilly, 1999a), but the triad of chronic widespread pain, fatigue and non-restorative sleep makes fibromyalgia highly likely. Further features that point to a diagnosis of fibromyalgia include the presence of other functional somatic manifestations such as chronic tension headaches and functional bowel disturbance, evidence of musculoskeletal tenderness on examination with

allodynia and hyperalgesia (suggestive of central pain sensitization), and psychological distress (*Table 2*).

Fibromyalgia is not a diagnosis of exclusion, however, which means that it is not mandatory for other conditions that cause widespread pain and fatigue to be excluded before a certain diagnosis of fibromyalgia could be made. Thus, one need not wait for a negative ANA (antinuclear antibody) or normal thyroid function result before offering this diagnosis. A confident diagnosis of fibromyalgia could be made on the basis of the clinical characteristics described in *Table 2* (Arnold et al, 2011).

It is important to note that fibromyalgia could coexist with another condition, and complicate the presentation. For example, about 10–20% of patients with rheumatoid arthritis or systemic lupus erythematosus may be additionally diagnosed with fibromyalgia (Wolfe et al, 1984; Middleton et al, 1994). Thus, the presence of features suggestive of rheumatoid arthritis such as synovitis, radiographic erosions, or positive cyclic citrullinated peptide antibody would not exclude fibromyalgia. Pain in such patients would be expected to be out of proportion to any joint inflammation, and escalating disease-modifying drug therapy alone is unlikely to improve symptoms.

Although the diagnosis of fibromyalgia generally becomes easier with longer duration of symptoms and presence of more suggestive features, differentiating it from certain forms of rheumatic disease can sometimes be tricky. For example, patients with systemic lupus erythematosus and fibromyalgia could both present with joint pains, tiredness, chest wall pain, cold hands, cognitive dysfunction, migraine headaches and even a positive ANA result (Suresh, 2007). Unless hard clinical features of systemic lupus erythematosus such as nephritis, haemolytic anaemia, thrombocytopenia, the characteristic malar rash, or specific autoantibodies such as anti-double stranded DNA or anti-Smith are present, diagnosis might be difficult. Likewise, patients with fibromyalgia might complain of dry eyes and dry mouth because of anxiety or autonomic dysfunction, and these features might be confused with Sjögren's syndrome.

Hence, while obtaining the history from a patient with chronic widespread pain, one should not only elicit positive features suggestive of fibromyalgia, but also those of other conditions that might coexist or with which it might be confused (*Table 3*).

What is the role of physical examination?

Although the diagnosis of fibromyalgia is made on the basis of the history, a thorough but focussed examination should be performed, especially during the first consultation. Apart from looking for signs of inflammatory or degenerative joint disease, thyroid disease, proximal myopathy or connective tissue disease, it is worth looking for evidence of regional pain problems such as rotator cuff tendonitis, lateral epicondylitis or tenosynovitis that might be amenable to local therapy such as corticosteroid injection or physiotherapy. It is important to treat what can be treated, and these conditions might easily be overlooked in patients presenting with widespread pain unless specifically looked for.

The American College of Rheumatology proposed classification criteria for fibromyalgia in 1990 (Wolfe et al, 1990). Patients will be said to have fibromyalgia if:

1. There is a history of widespread pain lasting >3 months
2. There is pain in 11 out of 18 tender point sites on digital palpation.

These criteria were mainly devised for use in research settings rather than for bedside diagnosis, but there is a general misconception that a diagnosis of fibromyalgia cannot be offered unless there are 11 out of 18 tender points. Although the sensitivity for the presence of 11 tender points is about 90%, specificity is only about 78%. Eleven or more tender points could also be found in about 5% of healthy individuals (Croft et al, 1994). Moreover, tender points do not capture the complexity of fibromyalgia. Hence, the more recent revised American College of Rheumatology diagnostic criteria for fibromyalgia published in 2010 excluded tender point examination, and included the other key features of fibromyalgia such as fatigue, unrefreshed sleep, cognitive dysfunction and associated functional somatic symptoms (Wolfe et al, 2010). A tender point count is, in fact, rarely performed in primary care, or even by many rheumatologists, and is not necessary to diagnose fibromyalgia.

Table 1. Some causes of widespread pain

Inflammatory arthritis (e.g. rheumatoid arthritis, seronegative spondyloarthropathy)
Polyarticular osteoarthritis
Connective tissue disease (e.g. systemic lupus erythematosus, Sjögren's syndrome)
Osteomalacia
Thyroid dysfunction (both hypothyroidism and hyperthyroidism)
Statin therapy
Multiple sclerosis
Malignancy (less likely with longer duration of symptoms)

Table 2. Clinical characteristics of fibromyalgia

Triad of chronic widespread pain, fatigue that is severe enough to limit daily activities, and non-restorative sleep
Presence of other functional somatic symptoms such as chronic headaches, functional bowel disturbance, irritable bladder and chronic pelvic pain
Psychological distress, and often a history of previous traumatic life events
Musculoskeletal tender points with allodynia and hyperalgesia (suggestive of central pain sensitization)
No characteristic abnormal laboratory or imaging test results

What investigations should be requested?

Fibromyalgia is not a diagnosis of exclusion, so unnecessary investigations should be avoided (Gialamas et al, 2003). These can reinforce the patient's fear that 'something is seriously wrong and the doctor hasn't yet found out what the problem is'. Indeed, no laboratory or imaging test is specific for fibromyalgia.

Some basic tests recommended by the FibroCollaborative (Arnold et al, 2011), a diverse group of leading experts in fibromyalgia, include full blood count, erythrocyte sedimentation rate, C-reactive protein level and a comprehensive metabolic panel (liver function tests, renal panel and thyroid function tests).

The relationship between serum vitamin D level and fibromyalgia is controversial. Vitamin D level has been shown to be lower among patients with fibromyalgia than controls, particularly among patients from Middle Eastern countries and the Indian sub-continent (Al-Allaf et al, 2003). However, other studies have shown no association between fibromyalgia and low vitamin D level (Warner and Arnspiger, 2008). Despite the absence of direct evidence of a link between fibromyalgia, it would be worth checking for concurrent vitamin D deficiency, especially in patients with risk factors such as Asian ethnicity, inadequate exposure to sunlight (e.g. elderly, house or nursing home-bound patients), malabsorption (e.g. coeliac disease), chronic renal or liver disease, and intake of drugs that increase the breakdown of vitamin D (e.g. phenytoin, rifampicin).

Autoantibody tests such as an ANA should not be requested unless the pre-test probability of systemic lupus erythematosus or other connective tissue disease is high (Suresh, 2007). Although a negative ANA result would almost exclude systemic lupus erythematosus because of its extremely high sensitivity (close to 100%), a positive result is by no means specific or sufficient on its own to make a diagnosis of systemic lupus erythematosus. When an ANA test is requested indiscriminately, the positive predictive value is only around 11%. Likewise, rheumatoid factor should not be requested

Table 3. Key aspects to cover in the history when faced with a patient with chronic widespread pain

Aspects	Notes
Extent of pain and specific troublesome areas	It is worth looking for evidence of regional pain problems such as rotator cuff tendonitis, lateral epicondylitis or tenosynovitis that might be amenable to local therapy such as corticosteroid injection or physiotherapy
Duration of symptoms	Chronic pain means that pain has been present for ≥3 months, but the longer the duration of pain, the higher the likelihood of fibromyalgia
Associated symptoms such as fatigue, unrefreshed feeling on waking in the mornings and cognitive dysfunction (memory disturbance and difficulties with concentration)	
Features suggestive of restless legs syndrome or obstructive sleep apnoea in those patients with sleep disturbance	Both restless legs syndrome and obstructive sleep apnoea have been noted to be more common among patients with fibromyalgia, and to result in greater sleep impairment (Stehlik et al, 2009; Viola-Saltzman et al, 2010; Prados et al, 2013). Detecting these problems might help to offer specific treatments
Presence of other functional somatic syndromes such as chronic headaches, irritable bowel syndrome, chronic pelvic pain or temporomandibular dysfunction	
Inflammatory joint symptoms such as joint swelling and prolonged early morning stiffness	Patients with fibromyalgia might also complain of 'swollen joints', but this would not be supported by objective evidence of synovitis. Early morning stiffness is not specific for inflammatory arthritis
Systems enquiry to detect extra-articular symptoms of other conditions that could present with widespread pain such as connective tissue disease, seronegative spondyloarthropathy or thyroid disease	Many features of connective tissue diseases might be confused with fibromyalgia or vice versa
Medication history (particularly statins)	
History of current or past psychiatric problems such as depression or anxiety	Any history of psychiatric problems such as depression should also be tactfully enquired about, preferably a little later during the consultation after some rapport has been established. It is important to be tactful because the patient is otherwise likely to feel that the symptoms are being dismissed as psychological ('These symptoms must be getting you down' is better than directly asking 'Do you feel depressed?')
Psychosocial stressors such as stressful life events, and physical or emotional trauma preceding onset of symptoms	History of traumatic past life events such as sexual abuse during childhood might strengthen diagnostic suspicion (Heim et al, 2000), but if there is only limited time available for consultation, it is best not to dig up unpleasant memories and make the patient leave the consultation room feeling more distressed than he/she was on entering
Family history of fibromyalgia or other functional somatic syndromes	First-degree relatives of those with fibromyalgia have an 8-fold greater risk of developing fibromyalgia than those in the general population (Arnold et al, 2004). Family members are also much more likely to be diagnosed with other functional somatic syndromes
Concerns, expectations and ideas about symptoms	Any unhelpful thoughts or ideas about symptoms should be explored so that this could appropriately be addressed with cognitive behavioural therapy

unless there is clinical evidence of an inflammatory arthritis. Positive autoantibody results should always be interpreted in the context of the whole clinical picture.

Conclusions

Fibromyalgia is a poorly defined chronic pain syndrome. Pathogenic mechanisms include central pain sensitization, altered deep sleep, and hypothalamic–pituitary–adrenal axis and autonomic dysfunction, aggravated by unhelpful thoughts, emotions and behaviours. Diagnosis is clinical, and based on the triad of chronic widespread pain, fatigue and non-restorative sleep, combined with evidence of other functional somatic manifestations, psychological distress, allodynia and hyperalgesia on examination, and absence of characteristic laboratory or imaging abnormalities. Investigations should be kept to the minimum, and requested mainly to exclude associated conditions. Management should involve a multidisciplinary approach, focussing on not only reducing pain, but also the associated sleep disturbance, physical deconditioning and psychological distress. **BJHM**

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KEY POINTS

- Fibromyalgia is a clinical diagnosis, characterized by a triad of chronic widespread pain with fatigue and non-restorative sleep.
- Patients with fibromyalgia also present with numerous other somatic symptoms such as chronic headache, functional bowel disturbance, irritable bladder and chronic pelvic pain.
- Psychological distress (anxiety and/or depression) is common among patients with fibromyalgia.
- Conditions such as rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, hypothyroidism and osteomalacia could mimic or coexist with fibromyalgia.
- It is important to look for evidence of regional soft tissue disorders such as lateral epicondylitis, capsulitis or plantar fasciitis, as these are amenable to local therapy.
- Treatable disorders that might contribute to sleep disturbance should be looked for, such as restless legs syndrome, obstructive sleep apnoea or carpal tunnel syndrome.

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