Common functional pain syndromes

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A01, A02, E03

Key points

- Functional pain syndromes (FPS) affect more than 15% of the population worldwide.
- Polymorphisms in the catechol-O-transferase gene are associated with FPS.
- Central sensitivity syndrome (CSS) may play a central role in FPS.
- CSS results from a complex interplay of genetic susceptibility and environmental influences.
- Future clinical trials based on pain phenotypes will allow targeted analgesic regimes.

Fibromyalgia

Introduction

FM is a common, debilitating somatic functional pain syndrome. FM is a misnomer as it is not due to connective tissue, or of pure muscular, pathology. Incidence remains high in the developed nations and it represents a significant financial burden. Advances are being made in our understanding of the genetic factors and resultant functional changes associated with FM. Currently, management options are still centred on symptom control.

Definition

As of 2010, the American College of Rheumatology updated its diagnostic criteria for FM (Table 1). The use of trigger points has been replaced by a scoring system totalling the number of reported areas of pain and their severity. It is predicted that these new criteria could result in a marked increase in the diagnosis of FM. Some scholars see the new criteria as a self-scoring system rather than a clinical tool.

Epidemiology

In the developed world, FM is estimated to have an incidence of between 2% and 7%. It affects both sexes but women more than...
The loss is more significant that mechanisms in the central nervous system amplify the input from peripheral nociceptors, probably due to a complex interplay between neurotransmitters that facilitate pain transmission and those that inhibit transmission of pain signals. This interplay would also explain other symptoms commonly present in those with FM like fatigue, memory problems, and sleep and mood disturbances.

Pathogenesis

There is no single ‘cause’ of FM. Best current evidence suggests an interplay of genetic and environmental risk factors leading to altered central pain perception. A number of consistent findings highlight the physiological and anatomical changes occurring. The pathophysiology of FM has been extensively covered in a previous article in this journal. New developments are mentioned below.

Genetic factors

FM has some genetic basis. First-degree relatives are 8.5 times more likely to have FM than relatives of patients with rheumatoid arthritis. Polymorphisms in catechol-O-methyltransferase (COMT) genes are associated with FM and there is correlation between the polymorphism and the number of tender pressure points that can be elicited clinically in these patients. A large study among twins demonstrated the concurrence of widespread pain among twins.

Functional neuroimaging

Functional magnetic resonance imaging (fMRI) has consistently demonstrated an increased response to stimuli in the insula and anterior cingulate cortex (ACC) in patients with FM. These areas are involved in the processing and perception of unpleasant pain signals. Evidently, they are experiencing heightened pain when compared with the healthy population. Morphometric analysis of FM patients via MRI shows a three-fold increase in age-associated grey matter reduction. The loss is more significant in areas correlating to stress, pain, and cognitive function. That could in part explain the flare-up that these patients can have during periods of emotional stress.

Investigations

The diagnosis of FM is mostly clinical as there is no definitive investigation that could confirm the diagnosis. However, since certain rheumatologic conditions such as rheumatoid arthritis may co-exist, there may be an indication for serologic tests in some patients. A complete blood count may be useful to rule out other causes of fatigue such as anaemia and leukaemia. Thyroid function tests need to be performed to rule out hypothyroidism as another cause of fatigue, if the condition is suspected.

Management

Initial management

Treatment is targeted at symptom control with efficacy measured by patient reporting. The initial approach includes patient education, graded exercises, and drug monotherapy. Randomized trials support educating these patients regarding the diagnosis and treatment of FM, the uncertainty of pathogenesis, and the importance of the patient’s own role in management. It is important to stress that FM is not ‘in the patient’s head’ and that it is ultimately a benign disease while acknowledging that there can be significant personal distress. Moderate, gradually introduced increases in physical activity show significant benefits in quality-of-life measures. Medications often commenced are

Table 1 American College of Rheumatology 2010 diagnostic criteria for FM

<table>
<thead>
<tr>
<th>2010 fibromyalgia diagnostic criteria</th>
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<tr>
<td>A patient satisfies diagnostic criteria for FM if the following three conditions are met:</td>
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<tr>
<td>1 Widespread pain index (WPI) ( \geq 7 ) and symptom severity (SS) scale score ( \geq 5 ) or WPI 3–6 and SS scale score ( \geq 9 )</td>
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<tr>
<td>2 Symptoms have been present at a similar level for at least 3 months</td>
</tr>
<tr>
<td>3 The patient does not have a disorder that would otherwise explain the pain</td>
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ascertainment

WPI: note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19

Shoulder girdle, left/right

Upper/lower arm, left/right

Hip (buttock, trochanter), left/right

Upper/lower leg, left/right

Jaw, left/right

Cheek

Abdomen

Upper/lower back

Neck

SS scale score

Fatigue

Waking unrefreshed

Cognitive symptoms

For each of the three symptoms above, indicate the level of severity over the past week using the following scale

0 = no problem

1 = slight or mild problems, generally mild, or intermittent

2 = moderate, considerable problems, often present and/or at a moderate level

3 = severe, pervasive, continuous, life-disturbing problems

Consider somatic symptoms in general, indicate whether the patient has:

0 = no symptoms

1 = few symptoms

2 = a moderate number of symptoms

3 = a great deal of symptoms

The SS scale score is the sum of the severity of the three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12

**Clinical presentation**

Patients with FM are likely to suffer from other concurrent conditions like headaches, dysmenorrhea, temporomandibular joint disorder, chronic fatigue, IBS and other functional gastrointestinal disorders, interstitial cystitis, endometriosis, and regional pain including back and neck pain. It is important for a clinician to distinguish between a new-onset pain from an unrelated etiology, and pain from FM presenting at a new site. What is perceived as touch in an individual from the general population is perceived as pain in individuals suffering from FM. This is probably due to their central sensitization. The term central sensitization implies that mechanisms in the central nervous system men by a ratio of 9 to 1. FM has a significant financial impact. European estimates have calculated FM patients cost €5000 per patient per year more when compared with a healthy reference group. With an incidence of 2% in the UK, that represents an annual financial burden of more than 6 million pounds through medical access and extensive comorbid overlap.

Table 1 American College of Rheumatology 2010 diagnostic criteria for FM
Common functional pain syndromes

tricyclic antidepressants (TCA) such as amitriptyline. In intolerant individuals, a serotonin–norepinephrine reuptake inhibitor (SNRI), e.g. duloxetine, could be utilized. The success of these medications in some patients with FM suggests that neurotransmitters play a vital role in the maintenance of symptoms.⁷

Refractory FM
Multidisciplinary input is crucial to the management of chronic, recalcitrant FM. Through the involvement of Rheumatologists, Psychologists, physiotherapists, and pain management specialists, FM patients can achieve a moderate reduction in pain intensity and improvement in quality-of-life scores.

Combination drug therapy is usually indicated and is customized to each patient. Side-effect profiles of the drugs need to be balanced to optimize symptom reduction and maintaining daily activities against some unpleasant effects of the prescribed drugs. Common combinations include a TCA or SNRI with an anticonvulsant such as pregabalin. Opioids are now widely recognized to be poor long-term options for FM management.

Irritable bowel syndrome

Introduction
IBS is a gastrointestinal disorder characterized by abdominal pain and altered bowel habits. It is the most common diagnosis in Gastroenterology and represents a significant financial and social challenge. There are two clinical forms: diarrhoea-predominant IBS which seems to be more common in men, and constipation-predominant IBS which is more common in women. Some patients may have mixed symptoms, with diarrhoea alternating with constipation. No conclusive ‘gut-based’ theory of origin has been demonstrated.

Epidemiology
Worldwide, it is estimated that 11% of the population suffer with IBS. UK prevalence of IBS is reported as anything between 7% and 21%. IBS affects women more than men with ratios varying from 1.5:1 to 3:1. Much like FM, IBS prevalence fades with age. Patients over 50 report less severe symptoms of a shorter duration.

Definition
Diagnosis follows the Rome III criteria (Table 2).⁸ NICE guidelines also recommend the use of exclusionary blood tests including full blood count, ESR, CRP, and anti-endomysial antibodies to rule out inflammatory bowel or coeliac disease.⁹

Pathophysiology
Initial research into the pathophysiology of IBS concentrated on bowel dysfunction itself. Investigation into factors such as bacterial overgrowth, food sensitivity, and altered immune response has proven to be of limited use thus far. A number of observations have been made that are starting to elucidate the disease process. Some patients have been noted to have alteration in intestinal permeability, and local immune function probably leading to a change in intestinal and colonic microflora.¹⁰

Visceral hypersensitivity
Visceral hypersensitivity has been elicited using a computer-controlled distension device known as a barostat. Many laboratories have proven that patients suffering from IBS have an increased sensitivity to rectal, bowel, and gastric stretch. Visceral hypersensitivity has been mooted as a potential ‘biological marker’ of disease.

Altered sensory modulation
IBS patients have been extensively investigated using fMRI and positron emission tomography (PET). There is altered activation in response to intestinal stimulation in the insula, dorsal anterior cingulate cortex (dACC), and prefrontal cortex.⁵

Genetic factors
There is evidence that a genetic component plays a part in the development of IBS. Twin studies demonstrate familial predictors of functional bowel diseases. Potential specific targets being investigated include serotonin transporter (SHTT) and G-protein (GNi3) polymorphisms. The SHTT SLC6A4 polymorphism in particular is significantly associated with the development of IBS.⁴

Management
Diet and lifestyle advice
Diet and lifestyle control are the first stage in symptom management. Advice includes regular meals, reducing caffeine, high fibre intake, limiting fresh fruit, and keeping oral fluid intake high.¹¹

Pharmacological interventions
First-line drugs largely target specific symptom relief. For those with diarrhoea-predominant IBS, antispasmodics and loperamide are prescribed. In constipation-predominant sufferers, laxatives are used. Second-line medications include inalclotide, a guanylate cyclase agonist that reduces activation of colonic sensory neurones, and TCA such as amitriptyline. SSRIs such as fluoxetine can also be administered if TCAs have no effect.⁸ The side-effect profile of centrally acting antidepressants can be used to good effect in patients who suffer from IBS. Since constipation is a known side-effect of TCAs, these could be prescribed for those patients who have diarrhoea–prominent IBS. Similarly, diarrhoea is a side-effect in patients who are on SSRIs, and those patients who have constipation-dominant IBS, may benefit from an SSRI.¹¹

Psychological interventions
NICE guidelines recommend the initiation of cognitive behavioural therapy in those with drug-resistant disease perpetuating beyond a year. Studies highlight multiple significant outcome benefits including a reduction in symptom severity scoring and the work and social adjustment scale. Currently, there is scant evidence for the use of acupuncture or reflexology.
**Temporomandibular dysfunction**

**Introduction**

TMD is a broad term that includes a variety of conditions affecting the jaw complex, both acute and chronic. Chronic or refractory TMD, although uncommon, is being investigated heavily for the genetic factors leading to its development. Care must be taken before labelling someone with TMD as having functional pain. The aetiology for the pain could be either articular (potentially amenable to Orthodontics or to surgery) or myogenic in nature, with the latter fitting more into the pattern of FPS.

**Definition**

TMD is characterized by spontaneous pain in the mandible and the muscles of mastication and the temporomandibular joint. It has become a collective term covering a cluster of individual disease processes that result in jaw pain. Terms also utilized include temporomandibular pain and dysfunction syndrome (IASP) and temporomandibular joint pain dysfunction syndrome (WHO).

**Epidemiology**

Estimates for TMD prevalence range from 3% to 15% in the Western population. It affects more women than men with a ratio of ~2:1. The peak onset occurs at reproductive age with a decline in prevalence in the older population. Approximately 31% of patients with TMD go on to become chronic sufferers with symptoms persisting beyond 5 yr.

**Pathogenesis**

It is unusual for TMD to exist as a sole entity as a cause of pain. Frequently, patients either have symptoms of FM or other regional pains like cervicalgia or migraine. No single external cause or trigger has been identified for TMD. Instead, a complex interaction between environmental influences and genetic predispositions lead to psychological distress and pain amplification, irrespective of the cause.

Advances in high-throughput genotyping methods have rapidly increased the understanding of genes that alter pain sensitivity and psychological distress. Particular examples include genes involved in the regulation of COMT, adrenergic receptor B2 (ADR B2), and serotonin transporter (SHTT). Three haplotypes of COMT have been uncovered that are associated with pain sensitivity and the likelihood of developing chronic TMD.

There is no single locus that defines the phenotype. The targets discovered thus far occur commonly in the healthy population. The resultant clinical phenotypes displayed are likely a result of a complex epigenetic interaction. Environmental influences alter gene penetrance e.g. stressful life events, are more likely to trigger depressive illness in those with functional polymorphism in the SHTT gene.

**Management**

**Non-pharmacological strategies**

Treatment consists of patient education, self-care, and psychological support. Education should focus on trigger avoidance, explaining the nature of the condition and discussing the long-term management rationale. Self-care is customized to the individual patient and includes relaxation and stress management, self-monitoring of symptoms, and supervised exercises.

**Pharmacological therapies**

There is scant evidence for the pharmacological management of TMD. Acute TMD responds to non-steroidal anti-inflammatory drugs, although care must be taken with long-term use. Benzodiazepines with longer half-life have been utilized to reduce nocturnal symptoms during the first weeks of pain.

Refractory disease responds poorly to classical analgesics and there is no evidence to support the long-term administration of opioids or benzodiazepines. TCAs have been utilized with benefit in chronic TMD, perhaps again pointing to the role of central neurotransmitters in potentiating the pain. A systematic review recommended the use of TCAs in TMD as a type B evidence.

**Chronic cardiac chest pain**

**Introduction**

CCCP is a visceral functional pain syndrome. It is a poorly defined syndrome with no globally recognized clinical definition that represents a small element in the spectrum of cardiac chest pain. Response to traditional cardiac medications is poor, although some success is being achieved applying a biopsychosocial approach to symptom management. This condition and its management has been reviewed extensively in a prior article in this journal.

**Definition**

The definition of CCCP remains unclear in both nomenclature and the clinical picture. At present, syndrome X, CCCP, and sensitive heart syndrome are used interchangeably to define the functional pain syndrome of angina pectoris without cardiac ischaemia.

Clinically, there is no official definition but most require anginal pain in the absence of irregularities on the arteriogram, no bundle branch block on resting or exercise ECG, and no evidence of diabetes mellitus, valvular disease, or cardiomyopathy. These criteria rule out several potential confounding factors.

**Epidemiology**

The epidemiology of CCCP remains unclear due to unclear definitions. If the above criteria are to be applied, the incidence of the disorder is estimated to be 13% of all patients presenting to a cardiologist with chest pain. Patients with CCCP have an increased use of health resources with 80% of patients reporting one or more hospital admissions over a 6 month period.

**Pathogenesis**

There is growing evidence through functional neuroimaging and examination of altered pain thresholds that CCCP involves altered central pain processing similar to that seen in other FPS.

**Functional neuroimaging**

Using PET with $^{15}O$-labelled water, syndrome X patients have comparable regional cerebral blood flow (rCBF) responses to dobutamine stress in the hypothalamus, thalami, and right frontal cortices. However, syndrome X demonstrated central chest pain compared with healthy controls. The pain is associated with increased rCBF in the right insula but reduced rCBF in the left insula and right cingulate cortex compared with healthy controls. These areas are involved in the processing and perception of unpleasant pain signals.
Psychological aspects

Compared with patients with true coronary artery disease (CAD), CCCP patients have greater anxiety, more stressful life events, and a tendency to seek reassurance, probably because the investigations are routinely reported as normal.

Altered pain thresholds

Patients with syndrome X demonstrate a reduced pain threshold compared with those with CAD or healthy controls when undergoing direct cardiac stimulation i.e. rapid rotation of an intracardiac catheter. They also demonstrate a reduction in pain thresholds with peripheral stimulation of the forearm.

Management

Management of CCCP requires a multi-departmental approach, including cardiologists, cardiac surgeons, pain specialists, psychologists, and Physiotherapists.

Therapies directed towards the heart

Many patients presenting with CCCP will have already received coronary revascularization with either percutaneous coronary intervention or coronary artery bypass grafts. Medical therapy typically consists of an anti-platelet medication e.g. aspirin, an angiotensin-converting enzyme inhibitor and a statin. They may also be on either β-blockers or calcium channel blockers. Medical therapy must be maintained and optimized to reduce recurrence of myocardial ischaemia.

Non-cardiac therapies

Imipramine, a tricyclic antidepressant, demonstrates a 52% reduction in chest pain episodes when compared with placebo. Spinal cord stimulators provide beneficial pain relief in ∼80% of selected patients with CCCP.5

Educational programmes such as the Liverpool Angina Management Programme (LAMP) can significantly improve patients’ quality of life. Patients learn about stress management, paced physical activities, dietary advice, and management of the emotional responses to angina. An important aspect of their education is the recognition that pain does not equal damage to the heart.

A unifying hypothesis

Traditionally, IBS has been managed by Gastroenterologists, FM by Rheumatologists, TMD by orofacial surgeons, and CCCP by Cardiologists. These traditional approaches have not proven to be very effective in a majority of these patients. By focusing only on the organ system most evidently affected, the global picture has been ignored.

It is becoming increasingly evident that no FPS is an island. There is extensive comorbid overlap and shared epidemiological spread among FPS. By analysing the similarities in genetic research, functional imaging, and management approaches, these conditions need to be examined under a new light.

Epidemiology

The four FPS examined are more common in women and their incidence reduces with advancing age. A likely explanation for this is the regulation of COMT activity by oestrogen. Higher concentrations of oestrogen in women affect COMT behaviour more than in men, thus amplifying the influence of polymorphisms. COMT activity alters with age, giving a possible explanation for the reduced incidence of FPS in the elderly population.14

Comorbid overlap

Extensive comorbid overlap has been demonstrated in these conditions described and the relationship between phenotype and genetic factors has been well studied in two large studies among twins. For example, it has been shown that the most accurate predictor of developing TMD is the presence of another FPS such as FM.6,15 Table 3 reveals the extent of overlap noted through epidemiological studies of FPS.16 This fact points to an element of shared physiological process contributing to the pathophysiology.

Genetics

FPS have been linked with polymorphisms of COMT, SHT transporters, and adrenergic receptor B2.6,15 An important mechanism of central regulation of peripheral pain inputs is the descending inhibitory pathway. Descending fibres originating in regions such as the periaqueductal grey matter modulate spinal inputs via noradrenergic and serotonergic nerve endings. A reduction in norepinephrine and SHT at the nerve synapses as a result of these polymorphisms could impair this process and increase pain perception.

Functional neuroimaging

FM sufferers demonstrate increased responses to both noxious and non-noxious stimuli compared with healthy individuals. Similar patterns involving the insula and ACC are seen in IBS and TMD sufferers. This suggests a reduction in the normal gating mechanisms of central inhibition.

Management

TCAs largely work by inhibiting serotonin and norepinephrine re-uptake, thus elevating synaptic concentrations. Subsequently, descending inhibitory pathways are bolstered, potentially reducing the negative effects resulting from the gene polymorphisms described above.

Increasingly, antiepileptics such as gabapentin are being used in the treatment of FPS. fMRI studies demonstrate a reduction in fMRI signatures of central sensitization with gabapentinoid use.18

Central sensitivity syndrome

These common FPS share, at least partly, an underlying mechanism. Although there are a variety of terms in circulation, the most suitable nosological term is CSS.19 Individuals have genetic susceptibility through a polygenic mix of common polymorphisms in genes such as COMT, SHTT, and ADRB2. This susceptibility does not automatically lead to an FPS. A complex network of epigenetic and gene–environment interactions lead to CSS development (Fig. 1).20

Environmental triggers may play a key role influencing what phenotypic facet of CSS presents to the healthcare system.

Table 3 Comorbid overlap of common FPS. FM, fibromyalgia; IBS, irritable bowel syndrome; TMD, temporomandibular dysfunction

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<th>Primary diagnosis</th>
<th>Degree of overlap with secondary condition (%)</th>
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<tr>
<td></td>
<td>FM</td>
</tr>
<tr>
<td>FM</td>
<td>NA</td>
</tr>
<tr>
<td>IBS</td>
<td>32–65</td>
</tr>
<tr>
<td>TMD</td>
<td>13–18</td>
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Increased peripheral input from the affected organ system, when coupled with CSS, results in the development of predominant symptoms in that system. Examples include hepatitis C and HIV being associated with FM incidence, gastroenteritis triggering IBS, and trauma to the jaw initiating acute and subsequently refractory TMD.

21 The future

Research
Unifying disparate research targets into one field will allow more rapid understanding of the complex gene–environment reaction. Techniques such as high-throughput SNP (single-nucleotide polymorphism) analysis promote rapid discovery of potential gene targets in those with CSS. These targets must then be analysed in large prospective cohort studies such as the Oral Pain: Prospective Evaluation and Risk Assessment (OPPERA) trials for TMD.

22 Targeted analgesia
By identifying pain subtypes through clinical trials, we will be able to identify responders to different treatment modalities. The patient’s phenotype can then be matched with a treatment responsive to that particular pain subtype and thus pain can then be treated more effectively with a targeted analgesic regime.

Until then, a combination of pharmacological, psychological, and self-help strategies will be the mainstay to treat FPS.

Declaration of interest
None declared.

MCQs
The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to BJA Education.
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