Dysfunctional syndromes and fibromyalgia: a 2012 critical digest

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ABSTRACT

Medically 'unexplained' chronic disorders remain a challenge for clinicians because the patients with these syndromes have a wide range of symptoms, including pain, impaired concentration, sleep disturbances, fatigue and mood disorders, as well as functional problems and difficulties in carrying out the activities of daily living.

Such disorders are the result of a complex physiological interaction of central and peripheral nervous signalling that leads to a highly individual symptom complex, although some of them seem to be related to one another, especially in terms of the mechanism of chronicity and pain amplification, and the co-occurrence of fatigue, sleep alterations, mood disturbances and cognitive impairment.

This review will discuss the recent literature concerning the most common dysfunctional disorders: fibromyalgia syndrome, myalgic encephalomyelitis/chronic fatigue syndrome, and irritable bowel syndrome.

Introduction

Medically 'unexplained' chronic disorders remain a challenge for clinicians (1) because the patients with these syndromes, including patients with fibromyalgia (FM) (2), irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), and a variety of other disorders (see Table I) (3), have a wide range of symptoms, including pain, impaired concentration, sleep disturbances, fatigue and mood disorders, as well as functional problems and difficulties in carrying out the activities of daily living (ADL) .

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Fibromyalgia (FM) is now considered a disorder of nociceptive processing (4). Growing evidence suggests that similar pathophysiological processes lead to hyperalgesia beyond the apparent anatomical focus of pain associated with regional pain syndromes such as temporo-mandibular disorder (TMD), irritable bowel disease (IBS), interstitial cystitis, or cervical and low back pain (5), and that they linked by a unifying pathological process of dysregulated nociception known as "central sensitisation". Given their shared pathophysiological mechanisms, these disorders have also been called "central sensitivity syndromes"(CSS) (6), although other pathophysiological mechanisms may play a role in different medically unexplained disorders (7). Environmental factors can influence their development, and a number of "stressors" may be temporally correlated with their onset, including trauma, infections (*e.g.* hepatitis C virus and Lyme disease), emotional stress, catastrophic events (*e.g.* war), autoimmune diseases and other pain conditions (2). The term *dysfunctional syndromes* is now preferentially used, and almost every medical specialty may express at least one of them.

This review will discuss the recent literature concerning the most common dysfunctional disorders: FM, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and IBS.

Fibromyalgia syndrome

FM is a chronic, generalised pain condition with characteristic tender points upon physical examination, often accompanied by a number of associated

symptoms such as fatigue, sleep disturbances, headache, IBS and mood disorders. Every year, a growing number of original articles, reviews and meta-analysis are published in medical journals and, for this reason, we will limit this overview of the FM literature to the papers indexed by PubMed from December 2011 to November 2012 (2).

Immunity system dysregulation and inflammation

The current data do not identify any distinct etiological or pathophysiological factors mediating the development of FM (7), which is associated with inflammatory rheumatic diseases, gene polymorphisms of the 5-hydroxytryptamine (HT) receptor, lifestyle factors (smoking, obesity, lack of physical activity), and physical and sexual abuse in childhood and adulthood, and is probably the result of various pathogenetic factors and pathophysiological mechanisms (8).

Despite the growing body of data concerning the pathophysiology and generation of pain, our knowledge is still limited. A pathogenetic role is probably played by the central sensitisation process, which is characterised by the development of chronic (central) pain and other associated symptoms (fatigue, stiffness, sleep disorders, cognitive and vegetative disturbance) (9).

Oxidative stress also seems to be involved, although it is not clear whether it is a cause or consequence (10). Recent studies by Cordero (11, 12) have shown that both mitochondrial dysfunction and oxidative stress may play a role. Low CoQ10 levels have been detected in patients with FM and it has been found that CoQ supplementation can restore biochemical parameters and induce a significant improvement in clinical symptoms (10). This suggests that inflammation could be a mitochondrial dysfunction-dependent event involved in the pathophysiology of FM and indicates mitochondria as a possible new therapeutic target.

FM patients may also have other concomitant functional pain syndromes, such as IBS, functional dyspepsia, TMD, interstitial cystitis/painful bladder syndrome, and CFS. The pathophysiological mechanisms of these disorders are not clear, but it has been hypothesised that they share a common pathogenesis and common pathophysiological mechanisms, including enhanced pain perception, altered regional brain activation, infectious etiologies, dysregulated immune and neuroendocrine functions, and genetic susceptibility (13).

Table I. Dysfunctional syndromes by specialty.

Allergy	Multiple chemical sensitivity
Cardiology	Non-cardiac chest pain
Dentistry	Temporomandibular joint dysfunction, atypical facial pain
ENT	Globus syndrome
Gastroenterology	Irritable bowel syndrome, functional dyspepsia
Gynaecology	Premestrual syndrome, chronic pelvic pain
Infectivology	Myalgic encephalomyelitis / chronic fatigue syndrome
Neurology	Tension headache
Pneumology	Hyperventilation syndrome
Rheumatology	Fibromyalgia
Urology	Interstitial cystis

Autoantibodies may be involved in the etiopathogenesis of FM. Tagoe *et al*. (14) have pointed out that there is considerable evidence to suggest that autoimmune thyroid disease (AITD) is closely associated with FM, and the results of the studies of Suk *et al*. (15) support the hypothesis that thyroid autoimmunity may influence its development.

Recent analyses of inflammation-related markers have confirmed that many FM patients have abnormal levels of a number of inflammatory cytokines, which may play a role in the syndrome's pathogenesis. Xiao Y *et al*. (16) found that serum high-sensitivity C-reactive protein (hsCRP) CRP levels are higher in patients with FM, and significantly correlate with body mass index (BMI), the erythrocyte sedimentation rate (ESR), and interleukin (IL)-8, and IL-6 levels, thus suggesting that inflammation may contribute to the symptoms of some FM patients, especially those who are obese. Weight loss and anti-inflammation therapies may be useful in the management of FM patients with high hsCRP levels. Bote *et al*. (17) have studied systemic inflammatory and stress responses, as well as the innate response mediated by monocytes and neutrophils, and found that FM patients had an inflammatory status accompanied by an altered stress response, mainly manifested by high circulating levels of IL-8, CRP (in 100% of the patients in the FM group) and cortisol, and increased systemic levels of noradrenaline (NA) and head shock protein (Hsp)72. There is also an increase in the monocyte release of inflammatory cytokines [L-1β, tumor necrosis factor (TNF)α, IL-6, IL-10, IL-18 and monocyte chemotactic protein-1(MCP-1)] and enhanced activation of neutrophil functional chemotactic, phagocytic and fungicidal capacities. The authors concluded that FM is sustained by inflammatory/stress feedback dysregulation.

In a recent study, Kadetoff *et al*. (18) assessed intrathecal concentrations of pro-inflammatory substances in FM patients for the first time. The activation of glia cells leading to high intrathecal cytokine and chemokine levels had been hypothesised in chronic pain syndromes such as FM, and the authors observed high cerebrospinal fluid and serum concentrations of IL-8 but not IL-1β. This is in line with the view that FM symptoms are mediated by sympathetic activity rather than being dependent on prostaglandin-associated mechanisms, and supports the hypothesis of glia cell activation in response to pain mechanisms.

Furthermore, in addition to improving the health-related quality of life of FM patients, a pool-aquatic exercise programme has an anti-inflammatory effect by diminishing the spontaneous production of pro- and anti-inflammatory cytokines, and decreasing circulating CRP levels (19).

Another recent study (20) has underlined the effects of early life risk factors that may increase the occurrence or severity of FM in later life. The authors observed that the experience of neonatal pain causes long-lasting changes in nociceptive circuitry and increases pain sensitivity as the body ages; that premature birth and the related exposure to stressors cause lasting changes in stress responsiveness; and that maternal deprivation affects anxiety-like behaviours that may be partially mediated by the epigenetic modulation of the genome – all of these adult phenotypes are strikingly similar to the symptoms of FM patients. In addition, childhood trauma and exposure to substances of abuse may cause lasting changes in the

Genetic basis of fibromyalgia

Recent evidence suggests that genetic factors may contribute to individual differences in pain sensitivity, the risk of developing clinical pain conditions, and the efficacy of pain treatments. The studies published in 2012 showed that FM is genetically associated with polymorphisms of catecholamine-O-methyl transferase (COMT), monoamine oxidases, alpha-1-antitrypsin (ATT), and dopamine and serotonin transporters (21-25).

Karakus *et al*. [26] explored the frequency and clinical significance of missense mutations and a common polymorphism of the Mediterranean fever (MEFV) gene in a cohort of Turkish patients with FM, and found that MEFV gene mutations and polymorphisms are positively associated with a predisposition to develop FM.

Sodium channels located in dorsal root ganglia (DRG) (particularly Nav1.7) act as molecular gatekeepers for pain detection. Nav1.7 is encoded in gene SCN9A of chromosome 2q24.3 and is predominantly expressed in DRG pain-sensing neurons and sympathetic ganglia neurons. A number of SCN9A sodium channelopathies can cause rare painful dysautonomic syndromes such as paroxysmal extreme pain disorder and primary erythromelalgia, and Vargas-Alarcon *et al*. (27) found that a disabling form of FM is associated with a particular SCN9A sodium channel gene variant, and suggested that some patients with severe FM may have a dorsal root ganglia sodium channelopathy.

Mergener *et al*. (28) have hypothesised that the T102C polymorphism of the 2A serotonin receptor gene (HTR2A) may predispose to FM, although studies of larger samples are required to confirm this.

Lee *et al*. (29) meta-analysed the associations between susceptibility to the serotonin transporter (5-HTT) gene-linked polymorphic region (5-HTTLPR) S/L allele, COMT val158Met, and the serotonin 2A (5-HT2A) receptor 102T/C polymorphisms, and found that this was true of the last but not of the other two. However, as the genetic studies involved only small numbers of patients, this meta-analysis cannot rule out the possibility that the COMT val158Met polymorphism and the 5-HTTLPR S/L allele play a role in FM susceptibility, and further larger studies are necessary.

FM and sexual dysfunction

Over the last few years, an abundance of scientific papers have led to sexual dysfunction being added to the disorders that are most frequently complained of by FM patients. Regardless of whether or not they are pathophysiologically related to FM, there is no doubt that FM patients are more prone to develop sexual dysfunction than healthy controls. The leading causes of this greater incidence of sexual problems include contact-avoidance behaviour due to tenderness, depression, fatigue and the effect of medications, but a history of sexual abuse may also be a factor as it is frequently reported by women affected by FM.

Although most of the articles published in 2012 concerned sexuality in female FM patients, Batmaz *et al*. (30), found that FM leads to impaired sexual function of male patients, and that this was particularly closely associated with age, widespread pain, and the quality of life. Rico-Villademoros *et al*. (31) evaluated sexual functioning in both female and male patients, and found that both groups had significantly worse all-dimension sexual functioning in than subjects without FM.

In a previous review (32), we underlined the fact that FM is closely associated with sexual dysfunction in women. The major findings related to decreased sexual desire and arousal, decreased experience of orgasm and, in some studies, increased genital pain. Yilmaz *et al*. (33) reported less frequent sexual intercourse in female FM patients than control subjects, and found that female sexual function was worsened by depression. Ablin *et al*. (34) observed that female FM patients were significantly more impaired in all aspects of sexual functioning than healthy controls, and that muscle tenderness (reflected by the tender point count) significantly and negatively correlated with the various parameters of sexual function.

The current data do not identify any distinct etiological or pathophysiological factors mediating development of FM but, besides being associated with inflammatory rheumatic diseases and gene polymorphisms of the 5HT receptor, it is also associated with physical and sexual abuse in childhood and adulthood (8). In addition to the stress related to the constant presence of chronic widespread pain, fatigue and sleep disturbances, psychological aspects certainly affect the sexuality of patients with FM. Moreover, the most widely used drugs may also negatively interfere with their sexuality and sexual function. It is extremely important to recognise the extent of this complex problem and adopt multidisciplinary therapeutic interventions to improve the patients' quality of life.

Conventional and alternative therapies

The papers published in 2012 show that no new pharmacological therapy was developed or tested, but there was a plethora of studies concerning alternative therapies.

As no pharmacological treatment is consistently successful, the recent guidelines state that the optimal treatment of FM requires a multidisciplinary approach with a combination of non-pharmacological and pharmacological treatments. Among the former, spa therapy is popular in many European countries, as well as in Japan and Israel. One of the

two studies of spa therapy published in 2012 (35, 36) was a review that found it seems to be effective and useful by reducing pain, improving function, and improving the patients' quality of life. Nevertheless, the methodological limitations of the available clinical studies, such as the lack of double-blind, placebo-controlled trials, preclude any definite conclusions. However, although spa therapy cannot replace conventional therapy, it can complement and may represent a valid alternative for patients who cannot tolerate pharmacological treatments.

Maddali Bongi *et al*. (37) used the Rességuier method (RM) and qigong (QG) with the respective aims of increasing the patients' awareness and control of pain perception, and improving their posture, respiration and concentration. The results showed that both protocols improve pain, disability, the quality of life, tenderness and anxiety, and that RM improves sleep and QG improves depression. Other recent studies have also shown that QG significantly improves FM symptoms (38, 39), but Chan *et al*. (40, 41) have declared that further vigorously designed large-scale randomised, controlled trial (RCTs) with validated outcome measures are needed to confirm its effectiveness.

The treatments offered at the Maharishi Ayurveda Health Centre in Norway are based on Maharishi Vedic medicine (MVM), a consciousness-based revival of the ancient Indian Ayurvedic medical tradition introduced by Maharishi Mahesh Yogi, the founder of transcendental meditation (TM). Rasmussen *et al*. (42) found that these treatments and the health promotion programmes offered at the centre lead to long-term reductions in FM symptoms.

Another study (43) highlighted the beneficial effects of adding hypnosis to group multi-component cognitive-behavioural therapy (CBT). The analyses showed that FM patients who received multicomponent CBT alone or with hypnosis experienced greater improvements than those receiving only standard care, and that adding hypnosis enhanced the effectiveness of multicomponent CBT.

Over the last 20 years, a growing body of research has led to the recognition of the health benefits of tai chi in various chronic health conditions. This ancient health art, a Chinese multi-component mind-body exercise, contributes to chronic pain management in the three major areas of adaptive exercise, mind-body interactions and meditation, and there is encouraging evidence that it benefits patients with a variety of chronic, particularly musculoskeletal, disorders. It may therefore modulate complex factors and improve health outcomes in patients with chronic rheumatological conditions. As a form of physical exercise, tai chi enhances cardiovascular fitness, muscular strength, balance, and physical function, and also seems to be associated with reduced stress, anxiety and depression, and an improved quality of life. It can therefore be safely recommended to patients with FM, osteoarthritis, low back pain or rheumatoid arthritis as a complementary and alternative medical approach to improve patient well-being. (44, 45).

Patients suffering from chronic pain are the most frequent users of alternative medicine (CAM) therapies, and meditation is the third most frequently CAM reported in a US survey. A review by Kozasa (46) indicates an improvement in FM-related symptoms in patients participating in a meditation-based intervention.

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

Chronic fatigue syndrome (CFS) is a relatively common condition characterised by profound disabling fatigue and a range of other symptoms. The term CFS has persisted for many years because of a lack of knowledge of its etiological agents and disease process. There are currently several case definitions (with different nomenclatures), but none of them has produced evidence demonstrating its accuracy or precision (47). However, the most widely accepted for research purposes remains the 1994 definition of the Centers for Disease Control and Prevention (48). The criteria include severe fatigue lasting longer than six months, with the presence of at least four of the following physical symptoms: post-exertional malaise; unrefreshing sleep; impaired memory or concentration; muscle pain; polyarthralgia; sore throat; tender lymph nodes; or new headaches. A clinical diagnosis can only be made after excluding other diseases.

The more recent research and clinical experience strongly suggest the presence of widespread inflammation and multi-systemic neuropathology, some authors believes that it is more appropriate to use the term 'myalgic encephalomyelitis' (ME) because it indicates an underlying pathophysiology. It is also consistent with the neurological classification of ME in the World Health Organisation's International Classification of Diseases (ICD G93.3) (49, 50).

Nacul *et al*. (51) investigated the epidemiology of ME/CFS in three regions of England, finding that it is not uncommon and represents a significant burden to patients and society. Vincent et al. (52) estimated the prevalence and incidence of CFS in Olmsted County, Minnesota, using the 1994 case definition and documented fatigue for six months and at least for of the eight CFS-defining symptoms, as well as symptoms that interfered with daily work or activities. The patients not meeting all of the criteria were classified as having insufficient/idiopathic fatigue. The overall prevalence and incidence of CFS and insufficient//idiopathic fatigue were respectively 71.34 per 100,000 persons and 13.16 per 100,000 person-years vs 73.70 per 100,000 persons and 13.58 per 100,000 person-years.

Anderson *et al*. (53) systematically reviewed 34 qualitative studies of the experiences of ME/CFS patients, the experiences of physicians, and issues involving both groups. They found that the development of ME/CFS affected patient identity, and reduced their functional and coping capacities; the physician-specific experiences indicated a lack of awareness of ME/CFS and led to a recommendation to improve educational resources; the joint issues showed that a diagnosis creates tension and fuelled the stigmatisation of ME/CFS.

It has been found that patients with CFS are much more passive than healthy sedentary control subjects, but there

was no evidence of major variations in the patients' activity patterns during the day, or day by day (54). It has also been found that patients with CFS have a higher prevalence of migraine with and without aura than healthy controls (55), leading to the suggestion that the pathogenetic mechanisms of migraine such as central sensitisation may contribute to the pathophysiology of CFS.

Clark *et al*. (56) looked for premorbid risk markers of CFS in the 1958 British birth control cohort and, after adjusting for psychopathology, found that parental physical abuse, childhood gastrointestinal symptoms and parental reports of many colds were independently associated with self-reported CFS/ME. They also found that female gender and premorbid psychopathology were the only risk markers of CFS-like illness, regardless of comorbid psychopathology (56).

Nater *et al*. (57) studied the impact of cumulative life stress on CFS in a population-based study that showed exposure to stressors was significantly more common in CFS patients than in non-fatigued controls; post-traumatic stress disorder was also significantly more common in the patients. In a study of the occupational and quality of life consequences of CFS in young people, Taylor *et al*. (58) found the subjects with CFS reported lower perceived competence, and impaired physical functioning, school performance, social activities, emotional functioning and general health. Santamaria et al. (59) found that the duration of illness dose not predict cognitive dysfunction in patients with CFS.

Piraino *et al*. (60) investigated the association between cytokine genes, fatigue, and other dimensions of the acute sickness response in 296 subjects (145 women, 151 men) acutely infected with Epstein-Barr virus (EBV), Ross River virus (RRV), or Q fever. The symptom domains were empirically based on self-reported symptoms, and included fatigue, pain, neurocognitive difficulties, and mood disturbance. The results showed unique genetic correlates of fatigue and the other symptom domains. After controlling for age, gender, and type of infection, the analyses showed that IFNγ + 874 was associated with increased fatigue, whereas IL10-592 and IL6-174 were associated with mood disturbances, thus supporting the idea that inflammation-related genes play a role in the etiology of fatigue in various contexts, and suggesting that the different dimensions of the behavioural response to sickness may have different genetic correlates.

Inflammatory processes and fatigue can also be influenced by psychosocial and behavioural factors. It has been shown that early life stress is a risk factor for inflammation in later life, as well as the development of fatigue, although only a few studies have examined the possibility that inflammation may mediate the stress-fatigue relationship (61). Cho *et al*. (62) tested this hypothesis in a community sample of 2716 white and Afro-American subjects aged 33-45 years (1484 women and 1232 men), and found that retrospective reports of early life stress were associated with high levels of fatigue at baseline and during a 5-year follow-up period.

Lattie *et al*. (63) studied 117 subjects with CFS enrolled in a stress management intervention (97 women and 20 men), and found that, as predicted, higher perceived stress management skills before treatment were associated with lower levels of fatigue; they were also associated with a steeper diurnal cortisol slope and lower levels of IL-2 (after controlling for age and gender), but not with the inflammation-related markers IL-1β, IL-6, TNF-α, or IL-10. They also found that the association between stress management and fatigue was mediated by distress, and suggested that stress management may lessen fatigue by reducing emotional distress. The association between stress management skills and fatigue was closest among the subjects with high levels of IL-6 (but not of other neuroimmune markers. These findings suggest that there may be subgroups of CFS patients who are more susceptible to the beneficial effects of stress management (63).

Plasma peroxide concentrations are significantly higher in patients with ME/CFS than in normal controls (64).

Tak *et al*. (65) made a meta-analysis of 85 studies, and found that baseline cortisol levels were not significantly different between subjects with functional somatic disorders (FSD) as a whole and healthy controls, but were significantly lower in subjects with CFS when the FSDs were considered separately. Kishi *et al*. (66) studied sleep stage transitions in CFS patients with or without FM, and suggested that CFS and FM are associated with different problems of sleep regulation.

Xenotropic murine retrovirus related virus (XMRV)/ and human murine leukemia virus related virus HMRV-like pro-viruses were not detected in peripheral blood mononuclear cell (PBMC) and plasma samples taken from Swedish patients with ME/CFS/FM or in sera from Swedish blood donors (67). Another study (68) found no evidence of XMRV nucleic acids, infectious viruses, or anti-XMRV antibodies in Canadian patients with CFS. Hohn and Bannert (69) have concluded that there is little to support the idea that XMRV is a retrovirus infecting humans or that it is clinically relevant in patients with prostate cancer or CFS.

Tomic *et al*. (70) observed that their CFS patients had higher levels of triglycerides (p=0.03), lipid oxidation product malondialdehyde (MDA) (p=0.03) and protein oxidation protein carbonyl (CO) (p=0.002) and lower levels of high density lipoprotein (HDL) cholesterol (p=0.001) than controls, but there were no significant differences in the levels of total protein, total cholesterol or low density lipoprotein (LDL) cholesterol. The CFS group had an unfavourable lipid profile and signs of oxidative stress-induced damage to lipids and proteins, which might indicate early pro-atherogenic processes in a group of patients who are otherwise at low risk of atherosclerosis. Anti-oxidant treatment and lifestyle changes are indicated for women with CFS, as well as closer observation in order to assess the degree of atherosclerosis.

Beaumont *et al*. (71) found that CFS patients showed no deficits in performance accuracy, but were significantly slower than healthy controls. CFS was further characterised by low and unresponsive heart rate variability (HRV),

greater heart rate (HR) reactivity and prolonged HR recovery after a cognitive challenge. Fatigue levels, perceived effort and distress did not affect cognitive performance. HRV was consistently associated with the performance indices and significantly predicted the variance in cognitive outcomes. These findings revealed an association between reduced cardiac vagal tone and cognitive impairment in CFS patients for the first time, and confirmed previous reports of diminished vagal activity.

Treatment strategies

Exercise treatment should be carefully and individually tailored to CFS patients, and have recently published by Van Cauwenbergh *et al*. (72) exercise therapy for people with CFS should be aerobic and must comprise of 10-11 sessions spread over a period of 4-5 months. In addition, people with CFS can perform home exercises five times a week with an initial duration of 5-15 min per exercise session. Moreover, the exercise duration can be gradually increased up to 30 minutes. Although a time-contingent approach may work for some patients, we recommend that exercise should be prescribed to maximise function while minimising post-exertional malaise.

Rimes and Wingrove (73) carried out a randomised pilot in order to assess mindfulness-based cognitive therapy (MBCT) in subjects with CSF who were still experiencing excessive fatigue after CBT, and found that MBCT was acceptable and manageable. Furthermore, it has been found that a multidisciplinary programme of combined CBT and graded exercise therapy offered in a tertiary rehabilitation clinic is effective for CFS patients (74).

Alreyk *et al*. (75) have systematicaly reviewed complementary and alternative treatments for ME/CFS patients on the basis of 26 RCTs involving 3,273 participants. The CAM therapies included mind-body medicine, distant healing, massage, tuina and tai chi, homeopathy, ginseng, and dietary supplementation. The results showed qigong, massage and tuina have positive effects, but not distant healing or homeopathy. Seventeen studies tested dietary supplements, but only NADH and magnesium were beneficial. The results of this systematic review provide limited evidence of the effectiveness of CAM therapy in relieving the symptoms of CFS.

Spitzer and Broadman (76) retrospectively reviewed 118 cases that were clinically consistent with CFS or FM and treated in a neurology practice. Sixty percent of the patients treated with oxybate experienced significant pain relief, and 75% experienced a significant reduction in fatigue.

Fluge *et al*. (77) carried out a double-blind, placebo-controlled study showing that B lymphocyte depletion using the anti-CD20 antibody (rituximab) is beneficial in CFS patients.

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder that is characterised by recurrent abdominal pain or discomfort combined with disturbed bowel habits in the absence of an identifiable organic cause. Visceral hypersensitivity has become a key hypothesis for explaining the painful symptoms in IBS and has been proposed as a "biological hallmark" of the condition

It has been demonstrated that a lifetime history of a wide range of major life traumas beyond those experienced in early childhood or of an abusive nature are associated with increased risk of IBS in women veterans, even after adjusting for their most frequent psychological comorbidities of depression and post-traumatic distress disease (PTSD) (78).

Suzuki and Hibi (79) reported that the overlap rate of functional dyspepsia (FD) and IBS could be in the range of 11–27%, and that overlapping FD and IBS is associated with more severe symptoms than either FD or IBS alone. It has also been found that restless legs syndrome is prevalent in patients with IBS, especially those with diarrheal symptoms (80).

Larson *et al*. (81) have reported that, despite the similarities in their symptoms, hyper- and normosensitive IBS patient have substantially different cerebral responses to standardised rectal distention, and that their expectations are consistent with differences in ascending visceral afferent inputs.

Probiotic Escherichia coli Nissle 1917 (EcN) has effects in IBS patients, especially those with altered enteric microflora (82).

Treatment options

It is known that fibre can increase transit time in IBS patients, but its therapeutic role is still controversial (83). A recent Cochrane review, which including subgroup analyses of insoluble and soluble fibres, found no statistically significant benefit associated with the use of fibre, and a separate analysis of studies with adequately concealed treatment allocation did not change the results (84).

It has been shown that physical activity is effective in treating conditions such as FM and CFS, both of which may co-exist with IBS. A recent RCT involving 102 IBS patients showed that increased physical activity improved gastrointestinal (GI) symptoms, and the authors suggested that physically active patients are likely to face less symptom deterioration than those who are physically inactive, and that physical activity should therefore be used as a primary treatment modality (85).

The efficacy of antispasmodics has recently been confirmed by Ruepert *et al*. (84) in a Cochrane review that found them effective in the treatment of IBS; the individual subgroups that were effective included cimetropium/dicyclomine, peppermint oil, pinaverium and trimebutine.

IBS patients have higher levels of anxiety and depression than controls. Antidepressants are effective in chronic pain conditions, and alter gastrointestinal transit time, and the same Cochrane review (84) found good evidence that they are effective in treating IBS. The subgroup analyses of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) were unequivocal and the effectiveness of the drugs may depend on the individual patient (84).

Agents acting on the 5-hydroxytryptamine (5-HT) receptor can improve smooth muscle spasms, abdominal pain, and changes in the bowel habits of

IBS patients. Alosetron, a 5-HT3 receptor antagonist, is licensed in the United States only for female patients with severe IBS, but a systematic review and meta-analysis of RCTs has shownd that alosetron, cilansetron and tegaserod are all effective (86).

Psychological disorders such as anxiety, depression and bipolar affective disorders are 2–3 times more frequent in IBS patients than in controls, and a Cochrane review has shown that psychological interventions may be slightly superior to usual care or waiting list control conditions at the end of treatment (87). However, only one study found them superior to placebo and the sustainability of their effect is questionable. Another meta-analysis and systematic review found that, although antidepressants were effective in the treatment of IBS, there was less high-quality evidence for supporting the routine use of psychological therapies (88).

Alternative therapies

One systematic review and meta-analysis of RCTs has found that patients reported greater benefits from acupuncture than from pharmacological therapies in Chinese trials (89). Herbal therapies such as iberogast (also known as STW 5, a combination of various plant extracts) and St John's wort, have also been evaluated in RCTs, but the latter was less effective than placebo (9).

New therapies for the treatment of IBS are emerging. Lubiprostone and linaclotide are drugs that act locally on chloride channels and guanylate cyclase receptors in the GI tract. They stimulate intestinal fluid secretion and accelerate transit by increasing chloride concentrations within the gastrointestinal lumen, and have now been approved in the USA for the treatment of IBS with constipation. It has recently been demonstrated that linaclotide 290 μg once daily significantly improves the abdominal and bowel symptoms associated with IBS and constipation over 26 weeks of treatment (91). Other emerging therapies include bile acid sequestrants (such as colesevelam), bile acid transporter inhibitors, and pancreatic enzyme supplements, all of which are under investigation (92, 93).

Conclusions

This paper reviews the recent literature concerning the three most common dysfunctional syndromes. These are defined by a variety of signs and symptoms that cluster in the different syndromes depending on which is most relevant or the specialist taking care of the patient. Epidemiological studies have demonstrated that 75% of FM patients meet the TMD criteria and 18% of TMD patients meet the FM criteria (94); furthermore, 32% of FM patients present with IBS and 32% of patients with IBS meet the criteria for FM (95). The perceived common aspects of TMD epidemiology, psychosocial risks, management and outcomes, combined with the absence of pathognomonic tests and overlapping symptoms, have historically led some researchers to suggest that their similarities outweigh their differences, and there is a persuasive body of evidence indicating sensitisation is a unifying pathophysiological mechanism. It has been proposed that these syndromes are characterised by the dysregulation of peripheral afferents and central nervous system pathways and, given their shared pathophysiological mechanisms, they have been called central sensitivity syndromes (CSS) (96). This underlying connection may not only explain why patients with these peripheral disorders sometimes develop widespread hyperalgesia, but may also provide a rationale as to why they overlap with one another (97). One current hypothesis suggests that the disorders emerge in an individual patient when a complex interaction of genetic predisposition, enhanced pain perception, and heightened psychological distress combines with certain environmental factors (98). However, some caution regarding the generalisability of the CSS tag is warranted, because the individual syndromes present as focal pain complaints, which may mean that each individual CSS is driven by a specific peripheral pain generator. Further research recognising the complex interplay between genetics, peripheral pain generators, dysfunctional pain processing, psychological factors, and environment triggers is essential to improve our understanding of why one subset of subjects develop FM and others develop CFS, IBS or other, rarer, dysfunctional syndromes (99-103).

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