Review

Algo-dysfunctional syndromes: a critical digest of the recent literature

R. Talotta[1], F. Atzeni[2], L. Bazzichi[3], C. Giacomelli[3], M. Di Franco[4], F. Salaffi[5], P. Sarzi-Puttini[1]

[1]Rheumatology Unit, L. Sacco University Hospital, Milan, Italy;
[2]IRCCS Galeazzi Orthopaedic Institute, Milan, Italy;
[3]Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Italy;
[4]Rheumatology Unit, Department of Internal Medicine and Medical Specialities, La Sapienza University of Rome, Italy;
[5]Rheumatology Department, Polytechnic University of the Marche, Ancona, Italy.

*Rossella Talotta, MD**
*Fabiola Atzeni, MD, PhD**
Laura Bazzichi, MD
Camillo Giacomelli, PhD
Manuela Di Franco, MD
Fausto Salaffi, MD, PhD
Piercarlo Sarzi-Puttini, MD

**These authors contributed equally to this paper.*

Please address correspondence to:
Fabiola Atzeni, MD, PhD,
Rheumatology Unit,
L. Sacco University Hospital,
Via G.B. Grassi 74,
20125 Milano, Italy.
E-mail: atzenifabiola@hotmail.com

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ABSTRACT

The etiopathogenesis of the algo-dysfunctional syndromes, which include chronic fatigue syndrome, fibromyalgia and irritable bowel syndrome, is still debated, but it is widely accepted that it is best described by a multifactorial model that include genes, environmental factors such as external infections, inflammation, dietary habits, impaired endogenous cortisol production, the aberrant activation of some areas of the central nervous system, and small peripheral nervous fibre damage. This complexity suggests that they should be managed by means of a multidisciplinary approach involving the use of both pharmacological and non-pharmacological treatments. The aim of this review is to discuss the most recent scientific acquisitions concerning these syndromes and their treatment.

Introduction

Algo-dysfunctional syndromes are a group of heterogeneous clinical conditions characterised by hyperalgesia and allodynia due to an abnormal sensitisation of the central nervous system (CNS) to pain without any signs of organic damage that includes chronic fatigue syndrome (CFS), fibromyalgia (FM), irritable bowel syndrome (IBS), interstitial cystitis, myofascial pain syndrome (MPS), temporomandibular dysfunction, restless leg syndrome, tension-type headache, migraine, dysmenorrhoea, pelvic chronic pain, and periodic limb movement disorder. All of these syndromes share an association between physical symptoms and an altered neuro-immuno-endocrine axis, but their diagnostic criteria exclude clinical pictures with an organic cause that may mimic them, such as hypothyroidism, HCV infection, Sjögren's syndrome (SS), etc.

This critical review considers the latest findings (published between September 2013 and September 2014) concerning the etiopathogenesis, diagnosis and treatment of the most important of these syndromes: CFS, FM and IBS.

Chronic fatigue syndrome

Chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) is a clinical condition that is prevalently characterised by fatigue lasting for at least six months, but also has a corollary of other symptoms such as a lack of restful sleep, headache, sore throat, muscle pain, cognitive disorders and lymphoadenopathy that finally converge to impair everyday life. It has a population prevalence of 0.4–1%, and mainly affects females.

Recent studies demonstrating epigenetic control of the transcription of some of the genes prevalently involved in the homeostasis of the immune response or metabolic cell processes suggest that genetics may contribute to the development of the disease. De Vega *et al*. (1) found a significant difference in the pattern of CpG methylation sites between 231 CFS patients and healthy controls (30% of hypomethylated sites in the patients and 70% hypermethylated sites in the controls, and the hyper- or hypomethylation prevalently occurred in the promoters or regulatory elements of the genes mainly involved in the immunological cascade.

It has also been shown that CFS patients have an altered immune response following physical activity, with a more intense oxidative stress, and the greater release of IL-10 and fragment C4a (2), and increased levels of IL-10, IL-1beta, TNF-alpha and IL-8 seem to be related to sleep disturbances and cognitive disorders (3). Brenu *et al*. found more regulatory T (T-reg) cells and B

memory cells in the peripheral blood of CFS patients than in the peripheral of healthy controls, suggesting the activation of the immune system against an antigenic stimulus (4). Cytokines may also induce nitrosative stress, thus damaging mitochondria and depleting ATP production (5).

The development of CFS may be favoured by microbial agents, as indicated by the fact its alternative name "myalgic encephalomyelitis" was coined to highlight the association between impaired brain tissue and an inflammatory stimulus supported by a viral or bacterial infection. It has long been thought that xenotropic murine leukaemia virus-related virus (XMRV) is involved in the pathogenesis of CFS, but Rasa *et al*. did not find any significant difference in the rate of nested polymerase chain reaction (nPCR)-detected XMRV infection between a cohort of 150 CFS patients and 30 healthy controls (6). Maggi *et al*. confirmed these data, in fact the XMRV was not found in 65 patients with CFS, 55 with FM, 25 with RA, nor in 25 healthy controls (7). However, viral infections can induce symptoms corresponding to those of CFS: one neurological review reported that 7% of parvovirus B19-infected subjects develop CFS (8), and other authors have found a correlation between the development of CFS and previous infections due to Giardia (9, 10) or *Herpes zoster* (11). It has therefore been suggested that a metagenomic approach should be used to identify the presence of microbiome belonging to new types of biologic pathogens presumably involved in the pathogenesis of CSF (12).

A recent meta-analysis investigating endocrinal alterations (particularly those involving the hypothalamic-pituitary-adrenal (HPA) axis has demonstrated a reduced cortisol awakening response in CFS patients (13). The HPA axis can be influenced by the milieu of cytokines released in the central nervous system (CNS), especially microglia. In an elegant murine experiment, Ifuku *et al*. found an increased concentration of IL-1beta and serotonin transporters in the prefrontal cortex associated with the development of fatigue (a decrease in running wheel activity) (14), and functional magnetic resonance imaging (MRI) of the brain has revealed that the activity of the caudate nucleus, putamen, and globus pallidus is impaired in CFS patients (15).

The development of CFS can be greatly conditioned by psychiatric status. Valero *et al*. (16) found that neuroticism (characterised by an anxious, guilty and shy personality) may worsen the severity of CFS, and this has been confirmed by Saez-Francàs *et al*. (17). Other factors associated with CFS include cardiovascular factors, such as a small heart and increased vascular stiffness (18, 19), and it has been reported that gluten intolerance is associated with both CFS and FM (20).

The diagnostic criteria for CFS vary widely from one consensus to another and, in an interesting study, Johnston *et al*. analysed the differences in laboratory and clinical functional measures (the Short-Form Health Survey (SF-36) and World Health Organization Disability Assessment Schedule II (WHO DAS 2.0) between CFS patients diagnosed on the basis of different consensus criteria and a control group: the patients had higher erythrocyte sedimentation rate (ESR) than the controls, and those diagnosed using the International Consensus Criteria had worse questionnaire and function scores, as if they represented a separate a separate subgroup with more severe disease (21).

It has recently been suggested that myalgic encephalomyelitis and CSF should be considered distinct clinical entities because of the differences in symptom severity (22).

Patients with CFS should be assessed using a multidimensional algorithm. Functioning, fatigue and related symptoms should be individually evaluated, although most studies are based on a brief and possibly incomplete clinical assessment (23). Cognitive disorders should be assessed using neuropsychological scales, as they are basic characteristics of the syndrome (24). Some authors have suggested evaluating the range of limb and spine movement by means of dynamic manoeuvres (25), and measuring the degree of global mobility.

However, there is still no univocal and objective consensus concerning the assessment of CFS.

The treatment of CFS is based on multidisciplinary interventions. Cognitive-behavioural therapy (26) and graded exercises form the basis of the therapeutic pyramid, and drugs are often used in association with non-pharmacological interventions. An Italian multicentre study of 741 CFS patients has compared the efficacy of corticosteroids, antidepressants, immunoglobulins and antiviral drugs, and found that the last two classes led to the best results (27). Given the complex pathogenesis of the disease, the indication for each pharmacological treatment based on the presence of a presumed infection, immune system activation, or aberrant central nervous system response.

Fibromyalgia

Fibromyalgia syndrome (FM) is a musculoskeletal disorder that affects 2–8% of the population. It is characterised by chronic widespread pain (lasting for at least three months) and other symptoms such as fatigue, neurocognitive deterioration and sleep disorders. The pain is related to aberrant nociception due to altered central or peripheral control and a positive feed-back mechanism that amplifies the sensation of pain (28).

FM may develop alone or follow other medical conditions such as connective tissue diseases, but its etiopathogenesis is still poorly understood. The contribution of genetics has recently been highlighted by the discovery of polymorphic variants of the catechol-O-methyltransferase, estrogen receptor alpha (29, 30) and opioid receptor μ1 genes (31) that seem to confer susceptibility. One interesting study was carried out by the Spanish group of Docampo *et al*., who analysed 313 female FM patients and 220 controls by means of genome-wide association scans (GWAS) and found an association between FM and some single nucleotide polymorphisms (SNPs) of genes coding for nervous system proteins such as neurexins or other transmembrane proteins involved in adhesion and synaptic functions (32). Synaptic integrity is sustained by various molecules and their qualitative or

quantitative alteration may underlie the disease's neurocognitive symptoms. Some authors have demonstrated a relationship between FM and an allelic variation of the SNAP-25 gene, which encodes a synaptic protein (33). Epigenetic modifications may also be responsible for a FM "genotype". The production of miRNAs following cytokine stimulation may affect the transcription of genes involved in both central and peripheral nervous signal transmitters (*e.g.* Na^+ or Ca^{++} channels or neuropeptides) (34).

Chronic inflammatory diseases play a special role in inducing and maintaining the vicious circle of nociception, which may initially originate from a specific anatomic site but finally extends to the rest of the body.

Neural plasticity due to a chronic stimulus such as inflammation may affect both the peripheral and CNS. Neuroglial cells are probably responsible for most of the neurochemical events occurring during the course of FM (35). An electroencephalographic study of 16 FM patients and 16 affected by osteoarthritis (OA) revealed a common pattern of activation in some of the cerebral areas involved in pain anticipation and nociception after the application of a painful stimulus, with the FM patients showing the more intense participation of the insula (36). Transcranial Doppler ultrasonography of 45 FM patients and 32 controls during a cognitive test demonstrated less blood flow in the middle cerebral artery and right lateralisation in the anterior cerebral artery (37), and functional brain MRI of 31 FM patients and controls receiving a painful stimulus revealed that the former showed an aberrant response in the dopaminergic/GABAergic mesolimbic nuclei that preside over reward or punishment mechanisms (38). Another functional MRI study has recently analysed CNS activation following auditory, visual or tactile stimuli, and the authors concluded that the 35 FM subjects showed less activation of sensory centres and greater activation of the insula in comparison with controls (39).

Psychiatric disorders such as anxiety or depression (40) and a lack of sexual satisfaction (41, 42), often accompany and worsen the course of the disease. An Indian study of 100 FM patients found that a loss of self-efficacy and inappropriate coping behaviour significantly correlated with a poor quality of life and the degree of pain (43).

In addition to the findings of the many recent studies of the mechanisms of central sensitisation to pain, it has recently emerged that the peripheral nervous system contributes to FM. Giannoccaro *et al*. have provided histological evidence of damaged small nerve fibres in 12% of 20 patients with primary FM (44). These data are in line with the results a study by Karo *et al*., who evaluated 41 FM subjects and 47 controls, and found a reduced epidermal nerve fibre density in the former, which correlated with to an increase in the serum levels of IL-2R but not IL-1, TNF-alpha or IL-6 (45). Serra *et al*. used the novel method of microneurography to assess the aberrant activation of C-fibres in 30 FM patients and two groups of controls: the microneurographic pattern of the patients included spontaneous nociceptor activity and hyper-excitability, and findings overlapping those characterising organic small fibre neuropathy, thus suggesting that peripheral nerve fibres may be involved generating FM symptoms such as dysesthesia (46).

The association between FM and previous or current infection is controversial (47, 48), thus suggesting that infections play a less important pathogenetic role in FM than in CFS. Nograha *et al*. showed that association between $CD3^+CD56$ natural killer and mood disorder in FM patients. These findings suggest a link between immune system and depression (49).

Like CFS, gluten intolerance (even without any laboratory or histological evidence of coeliac disease) seems to be related to FM insofar as symptoms may improve in patients on a gluten-free diet (50). Gluten intolerance may be a feature linking irritable bowel disease, FM and CFS, and there are many data supporting the efficacy of a gluten-free diet in improving the scores of scales such as the Fibromyalgia Impact Questionnaire (FIQ), the Health Assessment Questionnaire (HAQ) and the SF-36, and tender point (TP) counts (51). However, Tovoli *et al*. showed that prevalence of coeliac disease is the same in patients with FM compared that expected in general population (around 1%) (52).

Muscle anomalies such as increased interstitial lactate or glutamate concentrations assessed using microdialylitic techniques also seem to correlate with chronic widespread pain (53, 54) as it is known that lactate and glutamate can stimulate nociceptors.

Smoking is disadvantageous in FM because of its effects on the neuroendocrine system. A recent study by Bokarewa *et al*. has shown smoking is associated with a decrease in serum leptin levels and greater nociception in FM patients (55).

The pathogenesis of FM means that its management should be based on a complex algorithm. In pharmacological terms, it has recently been reported that memantine, which acts by blocking the N-methyl-D-aspartate (NMDA) receptor, had some beneficial effects in a cohort of 63 FM patients followed up for six months (56). It has also been found that melatonin, with or without amitriptyline, improved pain perception in a trial involving 63 FM patients (57). Non-pharmacological approaches such as acupuncture, exercise, balneotherapy or cognitive therapy may be helpful (58). However, a recent meta-analysis of the findings reported in 92 articles concerning FM treatments concluded that amitriptyline was the most appropriate despite the frequency of adverse events, whereas the studies of non-pharmacological treatments were generally weak and inconclusive (59).

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a widespread condition that may affect as many as one in five people, although the published prevalence rates depending on which classification criteria are used (60). Its most particular symptoms are abdominal discomfort and a change in bowel habit without any signs of an organic disease, and its pathogenesis can be traced back to an interplay of neuropsychological and biohumoral factors.

It has recently been ascertained that the disease is associated with the pres-

ence of some polymorphic alleles in the genes of the IL-1 receptor antagonist (IL-1RA) (61), the bile acid receptor (GPBAR1) (62), serotonin transporters 5-HTTLPR and SLC6A4 (63, 64), and IL-10 (65). The development of IBS can be prevented by epigenetic control as miRNAs regulating gene expression, cells proliferation and metabolic activities may also control the integrity of intercellular junctions in the gut (66), and one study has found that 43 IBS patients had increased serum levels of miR-150 and miR-342-3p (which are associated with inflammation and pain) in comparison with a control group (67).

Epigenetic modifications may take place after host/microbiota interaction, and anomalies in the immune system may lead to the overgrowth of some bacteria. It has recently emerged that the Toll-like receptors (TLRs) expressed on the surface of dendritic and intestinal epithelial cells that recognise many antigenic motifs deriving from microbiota may be important. TLR2 and TLR4 are generally under-expressed on intestinal epithelial cells under normal conditions, but their expression increases in the presence of inflammatory stimuli. TLR4-mediated signals lead to the separation of intestinal cells, increase permeability to bacteria, and induce the activation of NFkB (68), whereas apical TLR9 contribute to gut homeostasis and peripheral tolerance by inducing the production of IL-10 and suppressing the production of TNF-alpha (69). Alterations in intestinal flora may induce the over-expression of TLR4 and TLR2 and the under-expression of TLR9, and non-commensal bacteria may interact with intestinal and neural cells and influence gut functions.

There have been reports of some cases of IBS following intestinal infections. Jalanka-Tuovinen *et al*. analysed the composition of fecal microbiota in 57 subjects using a phylogenetic microarray and selected qPCR assays of rectum biopsies (70), and found that those who developed IBS had higher rates of *Bacteroidetes phylum* species than healthy subjects, an altered gastrointestinal barrier and more pronounced inflammation. A recent Danish case-control study investigating the presence of parasitic infection in fecal samples taken from 138 IBS patients discovered an increased prevalence of *Dientamoeba fragilis* and *Blastocystis* species (71), but these findings have not been confirmed by others (72).

A carbohydrate-rich diet is an aggravating factor as it facilitates bacterial fermentation, abdominal distension and pain. Similarly, IBS symptoms can be worsened by food allergies and gluten intolerance (73). An elegant study of histological and serum findings in 49 IBS patients and 30 healthy subjects by Vicario *et al*. showed that the former should a more marked expression of plasma and mast cells in jejune biopsies and produced more immunoglobulins (74).

There is considerable evidence showing that IBS is driven by a dysregulated neuro-immune-endocrine axis. O'Malley *et al*. stimulated rat mucosal plexus with mediators obtained from the plasma of IBS patients and controls, and found that neuronal calcium intake was increased in rats exposed to IBS plasma and typically inhibited by adding anti-IL-6 and corticotrophin releasing factor receptor (CRFR) 1 antagonist (75). The sympathetic and parasympathetic branches of the autonomous nervous system may influence gut activity via the brain/gut axis, particularly through the vagus nerve (76). A recent study of HPA axis activation and vagal tone in patients with IBS or Crohn's disease found that vagal tone inversely correlated with HPA activation and, in the IBS group, the production of epinephrine (77).

A functional MRI study of murine models of IBS evaluated cerebral activation following rectal stimulation, and found that the most involved neurological centres were the anterior cingulate cortex, the insula cortex, the prefrontal cortex and the thalamus (78), all of which areas involved in the elaboration of emotions and the reponse to pain. Stress, anxiety or depression contribute to the pathogenesis of IBS by activating the HPA axis and causing changes in sexual hormones (79, 80). Zhang *et al*. used a murine model of IBS to evaluate CNS activation after treatment with zymosan: the development of IBS was associated with the activation of the prefrontal cortex, the anterior cingulate cortex, the insular cortex and the amygdala, and the development of a behavioural anxiety that did not benefit from an intraperitoneal injection of NB001 (81).

The complex pathophysiology of IBS has led to it being treated in many ways depending on the symptoms, including diet, probiotics, antispasmodics and antidepressants, alone or in combination. The results of trials of various dietary regimens have generally been inconclusive. The data are conflicting, but one recent Australian study showed some benefit from a diet low in oligosaccharides, disaccharides, monosaccharides and polyols (82). Fibres and laxatives may sometimes help in alleviating gastrointestinal symptoms, with more evidence supporting psyllium hydrophilic mucilloid and polyethylene glycol 3350 (83), and a meta-analysis has found that use of probiotics (but not prebiotics) has some positive effects (84); a recent trial of *Lactobacillus plantarium* did not lead to any improvement in symptoms (85). The use of spasmolytic drugs such as simethicone, mebeverine or alverine citrate has a good ratio between efficacy and side effects (86), and otilonium bromide is also useful in treating spasms and abdominal pain as it reduces the contractility of the smooth muscle cells by inhibiting intracellular Ca^{++} influx (87, 88).

A recent meta-analysis has shown that the use of cognitive behavioural therapy, hypnotherapy and other psychodynamic treatments can be effective if combined with antidepressants (89).

The serotonin released by entero-chromaffin cells acts as a paracrine hormone that accentuates peristalsis, and it has been found that exendin-4, an analogue of glucagone-peptide-1, improves visceral pain in animal models probably by increasing serotonin transporter levels in colonic tissues (90). Riluzole (a neuroprotective agent involved in the reuptake of glutamate) proved to be more beneficial in improving visceral sensitivity in a group of 108 IBS patients than standard doses of mebeverine and amitriptyline (91). A trial involving 200 patients with diarrhoea-predominant IBS found that tandospirone, a partial

agonist of 5-hydroxytripatamine1A receptor, was efficacious and also alleviated anxiety (92), whereas trials involving patients with constipation-predominant IBS have shown that linaclotide was beneficial as it accelerated intestinal secretion and peristalsis (93). The use of antibiotics may also help in the case of constipation-predominant IBS, and a trial comparing the efficacy of neomycin alone and neomycin plus rifamixin in 31 patients with constipation-predominant IBS patients concluded that the combination of the two antibiotics was even more effective in relieving symptoms (94). Finally, a recent trial has shown that sacral nerve stimulation improved wall stiffness and mucosal sensitivity in a group of patients with diarrhoea-predominant IBS (95).

It therefore seems that a combination of pharmacological, dietary and psychological interventions is useful in managing IBS.

Conclusions

In conclusion, algo-dysfunctional syndromes have a variegated spectrum of manifestations but share the common pathogenetic mechanism of an alteration in the neuro-immune-endocrine axis. It is therefore recommended to use a multidisciplinary approach aimed at broadly controlling symptoms and improving the patients quality of life.

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