

Chronic Fatigue Syndrome (CFS) or “Systemic Immune Disorder” (SID)?

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Abstract

It is the opinion of the authors that the disease called chronic fatigue syndrome (CFS), or fibromyalgia, or myalgic encephalomyelitis, is primarily due to a disorder of the immune system and should rather be called “systemic immune disorder”. This disorder probably results from external factors such as inadequate stress adaptation, or a (retro)-viral infection deregulating the function of the memory T-lymphocytes in persons who are predisposed because of genetic or epigenetic alterations. Chronic inflammation with overproduction of cytokines, reactive oxygen and nitrogen species causes mitochondrial dysfunction with metabolic disturbance resulting in muscular and cerebral signs and symptoms.

The reference treatment consisting of cognitive behavioural therapy (CBT) and graded exercising (GET) considers CFS to be a somatoform disease, but was proven ineffective. Causal therapy should be directed toward restoring T-cell function and is now under assessment. Organ-directed treatment aims at improving stress tolerance, at reducing inflammation and oxidative stress, and at optimizing mitochondrial function by means of nutraceutical food supplementation. Symptomatic treatment uses antidepressants, sedatives and pain killers. Experimental treatments interfere with the immune system or attempt to activate brain metabolism, and need further assessment. Adverse effects of long-term medication must be avoided. In the opinion of the authors an acceptable therapeutic result can commonly be attained by combining meditation, such as mindfulness, adaptation of lifestyle and nutrition, with complementary food supplementation using nutraceuticals and plant extracts.

Keywords: CFS/ME; Chronic fatigue syndrome; Myalgic encephalomyelitis; Immune disorder; Nutraceutical; Complementary treatment

Introduction

“What’s in a name? that which we call a rose. By any other name would smell as sweet.” (William Shakespeare from Romeo and Juliet). The name given to a disease may be experienced as stigmatizing by the patients suffering from it. It is conviction of the authors that this is the case of the disease called by the purely descriptive name “Chronic Fatigue Syndrome” (CFS), particularly since this disease is commonly contributed to poor “stress-adaptation” [1] which is alleged to cause and “somatoform disturbances” [2] of psycho-psychological nature [3]. In Belgium, a multidisciplinary “care-net” was created to assist patients [4] based on the psycho-social treatment principle, in spite of the fact that an audit by the Belgian Federal Agency for Healthcare [5] had concluded that the effectiveness of this therapy is minimal, and not worth the cost [6,7]. The authors belong to the so-called “organically oriented clinicians”, who suggest that the signs and symptoms of CFS present resemblance with “Myalgic Encephalopathy or Myalgic Encephalomyelitis” [8] (ME, code G 93.3 of the WHO classification), and they consider CFS to be an organic disease the pathogenesis of which is multifactorial and only partly elucidated [9]. Although the disease classification index ICD-10-CM distinguishes between CFS and ME, these illnesses are commonly considered as one pathology in clinical practice. Based on recent literature and personal experience, the authors support the “organic” hypothesis since genetic, epigenetic,

immunologic and inflammatory aspects are decisive. The present opinion paper reviews the present state-of-the-art in favour of the latter factors, with immunological deregulation being of pivotal importance. It is suggested to change the name to “Systemic Immune Disorder” (SID for short). Changing the name of the disease may stimulate redirecting treatment options in the future.

Materials and Methods

According to Sackett [10], the “father” of modern evidence based medicine (EBM), the latter should integrate individual clinical expertise and the best external evidence. Within this concept the personal experience of the first author was integrated with references from the literature collected via PubMed and Google scholar, as well as articles derived from these. Results of diverse clinical trials are merged with knowledge gathered from epidemiology and physiopathology in order to create a logical consensus opinion (consensus based medicine).

Results

Clinical experience

The large majority of CFS patients can rather exactly situate the time as well as the circumstances of the beginning of their disease. Usually, the propaedeutic clinical examination does not reveal major abnormalities, except for possible signs of irritable bowel syndrome (IBS), with excessive gas accumulation in the colon as a symptom of

intestinal dysbiosis. Some patient's present signs of neuro-sympathetic deregulation such as (orthostatic) tachycardia, others have positive "trigger points" [11-13], or present lymphadenopathy in the neck region.

Whereas the "routine" blood analyses usually do not reveal abnormal values, the titres of IgG antibodies against external pathogens may be (extremely) elevated. This is commonly the case of antibodies against herpes 4 (Epstein-Barr virus, IgG anti-viral capsid antigen, VCA) [14], or against herpes 5 (Cytomegalovirus), or to streptococcus (elevated titre of antistreptolysin O; ASO). Also, auto-antibodies may be present, albeit in a low titre, such as antinuclear antibodies (ANF of ANA), or against thyroid tissue, namely anti-peroxydase and/or anti-thyreoglobulin antibodies. The fact that several antibodies are present simultaneously in the same patient suggests a disorder of the immune system to be involved rather than particular antigens [15].

The question to be answered is whether these biological changes are related to the complaints of the patients, and if so though which mechanisms this occurs.

Literature references on pathogenesis

The eminent French physiologist Claude Bernard (1813-1878) has stressed that diseases develop according to the principle "le grain et le terrain" (the seed and the soil) meaning that both the "inborn constitution" and an eliciting factor must be present to initiate pathology. Regarding the constitution genetics are important, but epi-genetic factors equally interfere. The latter depend on external elements such as nutrition, life style, exposure to (environmental) toxic substances, infections, emotional, socio-economical or physical stress, and others interfering with DNA- methylation or acetylation (Figure 1).

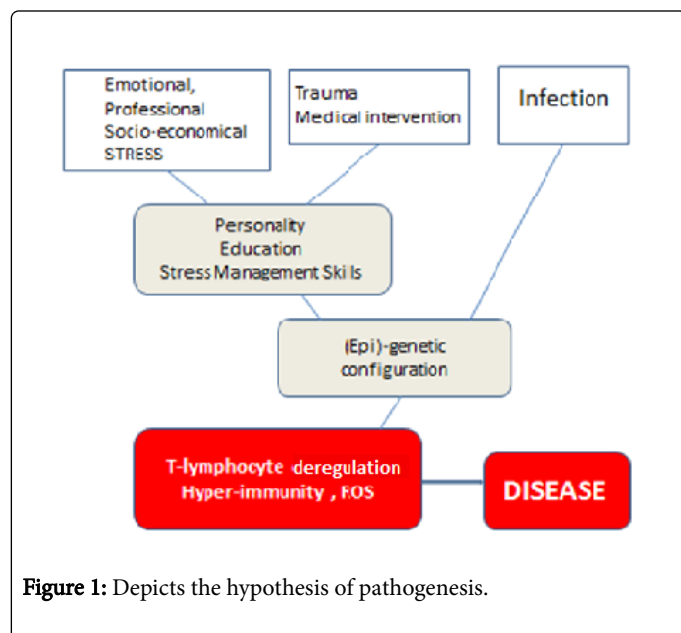


Figure 1: Depicts the hypothesis of pathogenesis.

Persons with limited "stress management skills", because of their personality, education, or other elements, are more susceptible to (long-lasting) stress or external factors such as trauma or a medical intervention inducing epi-genetic DNA changes. The latter may equally result from infection or unbalanced nutrition. Persons with a

particular form of genetic polymorphism or epi-genetic hyper-methylation may acquire deregulation of T-lymphocytes function excessively producing immunoglobulins. These induce chronic inflammation, with overproduction of reactive oxygen species (ROS) and nitrogen radicals. The inflammatory cytokines (mainly interleukins and tumour necrosis factor) and ROS cause the disease that may express itself primarily as chronic fatigue syndrome through mitochondrial dysfunction, with cognitive impairment, emotional, sympathetic and endocrine deregulation, and/or generalised muscle and tendon pain (fibromyalgia).

In 2010, Landmark-Hoyvik et al. [16] stated that studies on genetic and epigenetic factors in CFS patients were qualitatively unsatisfactory, but more recent publications have revealed "single nucleotide polymorphism" (SNP) in CFS patients [17]. For example, SNP was found to occur in the region that regulates for the COMPT (catechol-O-methyltransferase), which is related to immune function [18], but equally to neural activity in the prefrontal cortex and with epigenetic DNA-methylation [19]. In other patients SNP of the glucocorticoid-receptor gene (NR3C1) was detected [20]. Patterns of aberrant DNA-methylation were revealed in CFS patients, particularly in genes connected with the immune system, cell metabolism, and kinase activity [21]. These changes were especially evident after physical efforts, and may constitute the "soil" on which CFS develops.

Eliciting factors can be of diverse nature including physical, emotional, professional, socio-economical [22] and family-related events [23,24], or an accident, a traumatism, or even a medical intervention. All these have in common that they may cause important and long-lasting stress, which induces an inadequate reaction of the protecting heat shock proteins in CFS patients [25]. Such stress may cause excessive cortisol secretion by the adrenal glands and long-lasting elevated secretion of cortisol, temporarily suppressing immune resistance [26,27]. Subsequently, an exaggerated "rebound phenomenon" may occur with hyper-immunity [28,29] through the psycho-neuro-immune homeostasis [30,31]. Through this mechanism the production of the Immunoglobulin G against e.g. the Epstein-Barr virus by the memory-T-lymphocytes, goes into overdrive [32-34].

At the other hand, infections may cause a reaction characterised by altered activity of the lymphocytes [35-37] and of the granulocytes, which produce IgG antibodies and reactive oxygen radicals respectively. Among bacterial infections, *Borrelia burgdorferi* merits special attention since the so-called chronic form of Lyme disease may simulate CFS. The hypothesis of chronic Lyme disease is, however, a topic of controversy [38]. In general, the differential diagnosis between chronic Lyme disease and CFS can be made on the basis of history taking, whereas laboratory testing for *Borrelia* infection may be confusing [39,40]. In a small group of persons the diagnosis of "post-treatment Lyme disease syndrome" is proposed with complaints of fatigue, diffuse pain in the articulations and muscles persisting during more than 6 months after antibiotic treatment of the acute infection. It has appeared that, in these patients, the pathway of development and programming of the B-lymphocytes is disturbed in between 31% and 60% of the genes, with changes comparable to those seen in certain immune-mediated chronic diseases [41]. Hence, it is suggested that the post-Lyme syndrome may be due to an deregulated auto-immune response [39], explaining the similarity with CFS. This also clarifies why long-term antibiotic treatment is ineffective against disease progression.

At least in some patients with CFS a viral cause seems plausible [42]. Attention has been focussed particularly on the retrovirus human T

lymphotropic virus-1 (HTLV) and on the double stranded DNA herpes-6 virus [43]. The latter has also been associated with Hashimoto's thyroiditis [43-45] which is relatively common among CFS patients, and with the allegedly increased risk of cancer that has been observed in these patients [46], non-Hodgkin's lymphoma in particular [47,48]. A viral infection would also be compatible with the immunological and inflammatory changes that were recorded in many CFS patients [49], and which are expressed typically during the first 3 years of the disease [50]. According to some researchers the Epstein-Barr virus (Herpes virus 4) could trans-activate the human endogenous retrovirus K-18 (HERV-K18) [51], which acts as a super-antigen, and could evoke a hyper-immune reaction of the T-lymphocytes, enhancing the risk of auto-immune diseases [52]. At the other hand the Epstein-Barr virus presents molecular similarity (mimicry) that can induce anti-Sm (Anti-Smith) antibodies associated with auto-immunity [53].

Balanced opinion: it is plausible to suggest that inadequate stress-adaptation as well as infection can induce biological changes leading to permanent dysfunction of the lymphocytes, particularly among persons with a specific genetic or epigenetic constitution. These lymphocytes overproduce immunoglobulins [54] of the IgG class that bind with complement C3, which complex exerts cytotoxicity and provokes inflammatory reaction with the production of cytokines [55] including interferons [50]. Also the granulocytes are activated (over)-producing reactive oxygen and nitrogen species [56]. As part of the exaggerated and aberrant antibody production, Immunoglobulins may attack the body's own tissues initiating auto-immune diseases.

From pathogenesis to pathology

In our opinion it is reasonable to assume that the combination of the immunoglobulin-complement-complex, the inflammatory cytokines and interferon at the one hand and the oxidative overload at the other hand induce the complaints of CFS patients. Indeed, these agents impair the function of the mitochondria [57-60], resulting in disturbed enzymatic activity of the AMP-kinase [61], decreased production of adenosine triphosphate (ATP) [62,63], and precocious transition of aerobic to anaerobic metabolism. The latter results in the accumulation of lactic acid [64], among other things in the muscles, explaining the reduced muscular force, slower recuperation after an effort, and diffuse aching muscles [62].

Neuro-inflammation [65] and oxidative overload severely disturb cerebral function [66]. Permeability of the intra-cerebral capillaries may be increased as a result of oxidative and inflammatory damage to the vascular endothelium, by which the blood-brain barrier becomes less tight and inflammatory cytokines can seep through [67,68]. A similar process has been observed in the early phases of Alzheimer's disease [69]. Also, the mitochondria of the neurons become dysfunctional, causing the concentration of lactate in cerebrospinal fluid to increase [70]. In fact, broad-spectrum metabolomics has revealed a highly concerted hypo-metabolic response to stress that traces to mitochondria, with disturbed metabolism of sphingolipids, phospholipids, and glycosphingolipids in particular [71]. According to these authors, the abnormal metabolism bears some resemblance to the developmental state of "dauer" whereby (in animals) a stasis-equilibrium is attained that increases the resistance to external stress.

The oxygenation of the prefrontal cortex significantly decreases during physical exercise [72], while the microglia of astrocytes are activated associated with increased myelination in the prefrontal brain region [73,74]. Also abnormalities have been detected in the white

brain-matter of the curved bundle (fasciculus arcuatus) [75] as well as in the "resting-state functional connectivity" [76], which is considered a marker of the plasticity of the neural network. This then explains the cognitive problems and so-called brain-fog experienced by many CFS patients [77]. We suggest that the increased myelination in the prefrontal region is related to the abundance of neurons with short dendrites which try to compensate for the disturbed conductance through the curved bundle. In addition to the lowered cellular energy production because of mitochondrial dysfunction, the neurotransmission at the inter-cellular synapses is negatively affected by chronic inflammation and low-grade encephalitis [78].

These abnormalities are rather specific for CFS, and they have not been observed in case of fatigue due to cancer [79]. However, similar changes were noticed in war veterans suffering from the "Gulf war disease" [80] and in patients with "post-traumatic stress disorder" [81]. In addition, there is a correlation between the level of "stress management skills" at the one hand, and the degree of inflammatory reaction expressing itself by increased concentrations of the Interleukins 6 and 1 β , and the tumour necrosis factor alfa (TNF α) in blood, as well as with the neuro-immune processes causing fatigue at the other hand [82].

Quite remarkably the elevated concentration of these inflammatory cytokines has been demonstrated particularly during the initial period of the disease, but that after approximately 3 years there is a decreased concentration of the Interleukins 7 (that is important for the development of lymphocytes) and 16 (that is a chemo-attractant for immune cells), and of the Vascular Endothelial Growth Factor A (VEGF-A) [83]. In an experimental mice-model of auto-immune encephalomyelitis Interleukin 1 β in particular has been related to pain resulting from increased nociception [84]. This is associated with enhanced sensitivity of the peripheral and the central nervous systems for pain stimuli [84], which resembles to observations in fibromyalgia.

Several investigators have studied the cerebral blood flow in patients with CFS using different techniques, including single-proton emission computed tomography (SPECT) [85,86]. Blood flow through the limbic system and the hypothalamus was found to be significantly decreased in CFS patients [8]. This may possibly be related to the lower concentration of the Vascular Endothelial Growth Factor A [87] that was observed in patients with long-lasting disease [83]. The negative effect of the decreased blood supply may have been amplified by the elevated concentration of homocysteine [88] that was detected in cerebrospinal fluid of CFS patients [89]. The cerebral hypo-perfusion is similar, but not identical, to that seen in depressive patients, and is associated with functional disturbance of the basal ganglia and the thalamus-hypothalamic region [73]. We suggest that the latter could explain the deregulation of the day-night sleep pattern often observed in CFS patients. Together with the dysfunction of the amygdalae, it may also be related to the depressive mood that is sometimes observed in CFS patients.

It remains unclear whether certain neuro-sympathetic deregulations [90] such as orthostatic tachycardia [91] and irritable bowel syndrome (IBS) can be attributed to the dysfunction of the basal ganglia [92].

Recent studies observed altered composition of the gut microbiome [93], suggesting intestinal bacterial dysbiosis to play a role in the persistence of particular symptoms [94] via the microbiota-intestine-brain axis [95,96], with or without the mechanism of "leaky gut" [97]. In the so-called leaky gut syndrome the permeability of the intestinal wall for large molecules is increased. Large molecules normally do not

pass through the "tight junctions" (close connection between cells) of the intestinal endothelium. The leaky gut has been held responsible for the occurrence of several complaints, including chronic fatigue and joint pain. The leaky gut syndrome is rather common in patients suffering from severe inflammatory bowel diseases, but sometimes occurs in association with the irritable bowel syndrome. The leakage can be detected by means of the lactose/mannose test. In this test the person must drink a solution containing two sugars, namely one with a small molecular size being lactose, and one with a large molecular size being mannose.

Next, the amount of these two sugars is measured in the urine collected within 6 hours after ingestion of the solution. Normally, the urine will contain a lot of lactose, but little mannose. In case of increased permeability of the gut there is an excessive amount of mannose in the urine, and the diagnosis of leaky gut is accepted [98]. Whereas the evidence of intestinal involvement in the pathology of CFS seems to be rather solid, in our opinion the question remains whether the altered microbiome and gut dysfunction are the cause or the result of CFS.

Deregulation of the sympathetic nervous system is also held responsible for the changes in the capillaries that are sometimes detected by quantitative nail fold capillaroscopy [99]. The dilatation of the capillary loops [100] is considered to compensate for the decreased capillary diameter and density that occurs in CFS patients, and that may itself be related to the shortage of the Vascular Endothelial Growth Factor A [83].

Also, the hypothalamo-pituitary-adrenal axis may be deregulated [101] causing a lowered concentration of dehydro-epi-androsterone sulfate (DHEAS) and of the early morning concentration of cortisol [102,103]. The hypothalamic secretion of luteinizing hormone releasing hormone (LHRH) may be deficient which may be associated with disturbance of the menstrual cycle in women, or hypoandrogenism in men. Finally, the secretion of the anti-diuretic hormone may vary resulting in diuresis that importantly changes from day to day [104].

Autoimmunity against the thyroid causes Hashimoto's disease with hypothyroidism and elevated Thyroid Stimulating Hormone (TSH) concentration in blood.

The biological signs of increased immunity and inflammation were found to change during the course of the disease process. In general, they were most pronounced during the first 3 years, but they may persist afterwards. In addition, the intensity of the symptoms is not always correlated with the biological abnormalities, but auto-immunity due to re-programming of the memory lymphocytes, seems to persist.

Balanced opinion: The combination of oxidative radicals and the cytotoxic complex of immunoglobulin G-Complement C3 impairs mitochondrial function, reducing the production of Adenosine Triphosphate (ATP) with early transition of aerobic to anaerobic metabolism in muscles and in the brain. Accumulation of lactic acid explains muscular weakness and poor recovery after exercising. Cerebral capillary permeability is increased allowing the IgG-C3 complex to enter the brain and to cause inflammation (encephalitis or encephalopathy).

Aside from neuronal hypo-metabolism, inflammation disturbs synaptonemal transmission, particularly along the curved bundle, resulting in cognitive deficiency. Brain perfusion and oxygenation are decreased mostly in the prefrontal region, and in the basal ganglia

deregulating the neuro-sympathetic and endocrine systems, and causing emotional disruption.

Diagnosis

It is difficult to positively confirm the diagnosis of CFS. Several lists of major and minor criteria have been published and may be applied. It is our opinion that CFS remains in the first place an "exclusion diagnosis" that should be accepted only after other causes of the signs and symptoms have been carefully explored and excluded [105]. Meticulous clinical and biological evaluation is necessary in view of supporting the tentative diagnosis [106]. It is suggested to perform a number of immunological tests, and detect markers of inflammation. Also measuring markers of oxidative overload should be useful, and testing for SNP's and epigenetic alterations may be considered. Whereas assessment of the gut microbiome has been suggested to ascertain the diagnosis in up to 85% of cases [93], study of the broad-spectrum metabolomics in plasma may constitute an even more precise diagnostic tool [71]. Nonetheless, there is presently no single test that allows proving or rejecting the diagnosis of CFS with 100% certainty. The diagnostic criteria should be considered a useful tool, but they should be completed taking into account recent findings regarding genetic and epigenetic aspects, and the insight into immunological and inflammatory mechanisms as well as brain function.

Balanced opinion: Diagnostic criteria may be helpful to suggest CFS but the diagnosis should only be accepted after other diseases have been excluded. Markers of immune deregulation, of inflammation, and of oxidative overload may be detected upon blood analysis. Also biological changes suggesting present infection should be identified. Testing for genetic or epigenetic alterations, for abnormalities of the gut microbiome or metabolome offers new interesting diagnostic possibilities, but is probably too complicated and costly to be routinely implemented.

Treatment

The treatment of CFS remains a topic of controversy, and there is no "passe-partout" solution that is suitable for all cases. Treatment should be adapted to every individual situation, depending on signs and symptoms. The principle of "primum non nocere" (first do no harm) must prevail, and there is no final curative treatment available today.

For many years the reference treatment has been cognitive behavioural therapy (CBT), which was usually complemented with graded exercise therapy (GET). Other proposed treatments are specialised medical care, but also non-medical care by adaptive pacing, pragmatic rehabilitation, or supportive listening. The 3 latter treatments were considered unlikely to be sufficiently effective to warrant recommendation [107]. In contrast, the PACE trial (in the UK), applying CBT and GET, has reported significant improvement of fatigue and physical functioning [108]. Also, the frequency of muscle and joint pain was reduced, though the size of the effect was small [109]. The outcome of the PACE trial suggests the number needed to treat (NNT) to prevent physical deterioration would be approximately 14 [110]. The frequency of adverse events was not significantly increased by treatment [110]. However, in a similar controlled study in the Netherlands [111] objective parameters, such as employment status, decreased from 18.3% to 14.9%, with the proportion of patients living from sickness allowance increasing from 54% to 57% after one

year. There is no evident explanation for the striking difference between the results of the trials in the UK and in the Netherlands [112].

When comparing the long-term outcome after an average of 31 months of different treatments applied in the PACE trial, improvement of physical functioning and fatigue reported by participants was similar in those treated by CBT (Chalder fatigue questionnaire score: -2.2), by GET (-1.3), by adaptive pacing treatment (-3.0), or by specialist medical care (-3.3) [108,113]. Clearly the duration of follow-up is of pivotal importance, and the balanced opinion should be that the treatment approach using CBT with or without GET is not cost effective [5].

Causal treatment may be directed against the alleged viral infection using long-term intake of Valacyclovir that was found successful in approximately 85% of patients with high titres of IgG antibodies to herpes virus 6 (T-cell lymphotropic virus) and herpes 4 (Epstein-Barr virus) [114-117]. We do prescribe long-term Valacyclovir treatment in patients with a high titre of IgM antibodies to EBV, indicating recent infection that is probably still active. As far as we know, there have been no trials of medication against retroviruses [118-120].

The possible usefulness of long-term antibiotic treatment against bacterial infections, *Borrelia* in particular, is questionable [121]. It is not recommended for the treatment of the so-called chronic Lyme disease [39].

Adaptation of the way of life, and the family, social and professional environment is necessary in order to reduce stressful factors to such an extent that the limit of the capacity of stress adaptation is not exceeded. The stress management skills can be improved by means of techniques of relaxation and meditation such as Zen-yoga, transcendental meditation, autogenous training or mindfulness [122,123]. In the long term, mindfulness seems to be more beneficial to patient well-being than cognitive behavioural therapy (CBT) [124,125].

Aside from the recommendations concerning a "healthy life style" dietary prescriptions should be given, tobacco use must be prohibited, alcohol consumption should be limited, and moderate exercising should be encouraged. Many patients experience benefit from water-aerobics (aqua-gym) which they prefer to "graded exercise therapy" (GET).

Organ-directed treatment aims at correcting and suppressing the immune disorder by depleting the B-lymphocytes using infusions of the monoclonal antibody Rituximab (Mabthera®, Roche). This treatment has resulted in moderate to important improvement of fatigue in two thirds of patients [126], but needs to be repeated at intervals in some patients. At present, a large multicentre trial is ongoing including a higher number of patients. The cost of treatment and potential adverse effects constitute major limitations to its more general implementation.

Treatment with immune-modulators, such as hydroxychloroquine or azathioprine, has not been tested so far, but intatolimod treatment (a Toll-like Receptor-3 agonist that interferes with the production of Interferon-1) was found efficient in one third of patients [127].

Gamma globulin administration was reported to be either ineffective [128,129] or slightly effective, when given together with anti-viral treatment [130].

In some patients with decreased cortisol response to stress and deregulation of the day-night variation of the hypothalamo-pituitary-adrenal axis [101,102] the effect of treatment with a substitution dose

of cortisol was explored. The outcome was, however, limited [130], and did not even match the well-known side effects of long-term corticoid treatment [131]. Also, patients using this treatment should be warned that they may risk severe shock when under stress, during surgery, or after an accident. In contrast, patients with low concentration of dehydro-epi-androsterone sulphate in blood taken in the morning, may benefit from substitution with DHEA given in a dose of 20 mg to 50 mg per day, to be taken after breakfast in order to mimic the physiological day-night variation.

Hypothyroidism due to Hashimoto's disease must be treated *lege artis* with an adequate dose of L-thyroxine, sometimes combined with trijodothyronine.

Treatment with intermittent high-dose intravenous methylprednisolone infusions is inspired by the treatment applied in patients suffering from chronic inflammatory demyelinating polyneuropathy (CIPD) [132], and has offered relieve to some patients with fibromyalgia.

Symptomatic treatment usually combines antidepressants (commonly amitriptyline), with a sleeping pill, a muscular relaxant, and pain killers varying from paracetamol to opiates. After some time this approach becomes ineffective, while being addictive and impairing cognitive functions [133]. Non-steroidal anti-inflammatory agents (NSAI) may rarely relieve acute pain, but they are not indicated for long-term treatment [134].

Gabapentine en Pregabalin have been registered for the treatment of neuralgic pain [133]. These anti-epileptic drugs are, indeed, rather effective in fibromyalgia [135-137], but patients often interrupt treatment because of adverse effects such as sleepiness or dizziness [138].

A series of intramuscular injections of high dose vitamins B (cyanocobalamin, plus pyridoxine and thiamine) may temporarily reduce fatigue, and it can be repeated a few times per year.

Complementary and alternative treatments [139] include osteopathy or acupuncture, but nutraceutical food supplementation provides the strongest general supportive effect [9]. The product we have developed (Improve®, Nutriphyt, Oostkamp, Belgium) aims at interfering with 5 aspects of the disease, namely: (1) antagonising oxidative stress, (2) reducing inflammation, (3) optimising mitochondrial function, (4) improving stress adaptation, (5) decreasing epigenetic DNA-methylation. This is achieved by combining diverse plant extracts with vitamins [140], minerals and amino acids, including the antioxidants astaxanthine (acting on items 1 and 2) and ubiquinone Q10 (1 and 3) [141,142], seleno-methionine (5), zinc-picolinate (2), the natural anti-inflammatory pine bark extract containing anthocyanidins (2), l-acetyl-carnitine (3) [143-145], the phyto-adaptogen *Lepidium meyenii* (4) [146] or *Rhodiola rosea* (4 and 5) [147], and vitamins B6, B9 [148] and B12 (5). This nutraceutical has no side effects [149] and it is made complete by the intake of the long-chain poly-unsaturated omega 3 fatty acids docosahexaenoic (DHA) acid and eicosapentaenoic acid (EPA) [150,151].

The sleep pattern can be improved by melatonin [152,153] which also may enhance the pain-reducing effect of amitriptyline in patients with fibromyalgia [154]. The effect of Melatonin can be reinforced by adding the extracts of *Crataegus* (hawthorn) [155] and/or *Passiflora incarnata* (passionflower) [156].

Patients presenting the "leaky gut" may benefit from a food supplement (Mucoperm®, Nutriphyt Ltd, Oostkamp, Belgium)

composed of several vitamins, zinc [157], digestive enzymes, pH-regulators, oligosaccharides, and substances that optimise the intestinal microbiome [97]. Some patients experience benefit from the regular intake of probiotics or baker's yeast (*Saccharomyces cerevisiae*) that restore optimal gut microbiome, when accompanied by optimised dietary habits. This is particularly the case in patients with irritable bowel syndrome.

Experimental treatments: At present repetitive transcranial magnetic stimulation (rTMS) [158,159] is being applied to a number of patients, since this technique was reported to be successful in cases with therapy-resistant myofascial pain [160] or depression [161].

In specific cases, with signs of white-matter encephalopathy, neurotransmission and neuron function may possibly be improved by 4-amino-pyridine, the beneficial effect of which has been documented in some patients with multiple sclerosis [162]. It is, however, too early to make any suggestions about the potential effectiveness of these treatments in patients with myalgic encephalopathy.

Balanced opinion: The efficiency of different methods of treatment reported in the literature varies between hardly 20% and up to 90%, largely dependent on the criteria that are used to assess the degree of success [163]. In our experience the combination of the adaptation of the way of life and the diet, together with mindfulness, nutraceutical food supplementation, and water-aerobics is well-accepted by the patients, and commonly results in a sufficient recovery to allow for the majority of patients to resume work, albeit commonly in a part-time mode only.

Conclusions

Systemic immune deregulation with excessive T-cell-mediated immunoglobulin response is of pivotal importance in the pathogenesis of fibromyalgia/chronic fatigue syndrome. Therefore, it is suggested to rename this disease "systemic immune disorder". The hypothesis that exclusively incriminates stress maladaptation and neuro-sympathetic dysfunction seems obsolete since these can only explain part of the pathogenesis. Hence, the purely psycho-somatic therapeutic approach with cognitive behaviour therapy and graded exercise generated little, if any, benefit to the patients. Moreover, this so-called standard treatment is sensed as stigmatising by the patients. While awaiting more efficient causal therapies and knowing the remarkably diversity of the disease, tailor-made organ-directed and complementary treatments should be favoured.

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