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Chronic Fatigue Syndrome
Probable Pathogenesis and Possible Treatments

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Abstract

Chronic fatigue syndrome (CFS) belongs in the medically unexplained illnesses. It affects approximately 0.2–0.7% of the population in Western countries. It is characterised by unexplained fatigue, lasting 6 months or more, impairment of neurocognitive functions and quality of sleep, and of somatic symptoms, such as recurrent sore throat, muscle aches, arthralgias, headache and postexertional malaise. No link between infections and CFS has been clearly established but the immune system is activated, there are aberrations in several hypothalamic-pituitary axes and involvement of other parts of the central nervous system. No specific treatment has been found. Cognitive behavioural therapy is established to be of value to improve quality of life. More effective treatment should result, as advances in biomedical as well as psychological research continue.

Medically unexplained illnesses are an area of interest for clinical research for several reasons. Certainly an individual's suffering causes empathy and the desire to successfully treat the illness. The treating physician is curious, and wants to understand the cause and consequences of the underlying disorder. The biological background for the sense of fatigue is thus a research area of interest. Finally, the economic burden placed on society is substantial, and should result in prioritisation of this field of research.

The concept of the illness today named Chronic Fatigue Syndrome (CFS) has been an intriguing one. It is very possible that this syndrome was a subpopulation of the diagnosis neurasthenia; one of the most frequently diagnosed conditions in medical practice[1] yet a term that had seemed to disappear after the First World War. Since the American neurologist Beard published a noted paper in 1869 on the subject, the arguments concerning cause, diagnosis and treatment have been discussed in a recurring manner. This is mirrored by the number of names used for this condition, for example, epidemic neuromyasthenia, myalgic encephalomyelitis, Icelandic disease, Royal Free disease, post-viral fatigue syndrome, chronic mononucleosis and CFS. Some of these names indicate that at times an illness like CFS has occurred in an epidemic form; however, most cases today are sporadic. The origin of this illness has been and is as yet unknown.

In this paper we give a comprehensive overview of the field of CFS. We review probable pathogenetic mechanisms and treatments that have been studied as well as treatments in general clinical use. As this is a rapidly evolving area of research we highlight certain aspects with a focus on interference with microbes. This should be considered a general introduction to the field for clinicians.

1. Clinical Definition and Prevalence

The case definition of CFS was established in 1988[2] at the Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA and revised by an international working group in 1994.[3] The earlier definition focused more on physical findings such as fever and enlarged lymph nodes, as well as somatic symptoms, whereas the revised definition focuses on symptoms of inflammation, cognitive complaints and exercise induced relapse, resulting in a more inclusive case definition. The 1994 consensus case definition was necessary in order to make international comparisons between studies because varying definitions for CFS were in use (e.g. the Oxford-criteria, the Australian criteria). This 1994 case definition is now used globally.

The CFS case definition stresses the appearance of somatic symptoms but does not exclude psychiatric disorders such as anxiety disorders and milder forms of depression. See table I. This definition is based on expert consensus; no objective measurements are used, only symptom criteria as described by the patient. The main criterion is one of persisting or relapsing fatigue of at least 6 months duration which is new or has a definite onset (e.g. not lifelong), is not relieved by rest or resulting from ongoing exertion, and results in a substantial reduction in activities (occupational, educational, social and/or personal). In addition, a medical investigation will reveal no medical explanation. If these two main criteria are met, and there are no exclusionary illnesses, then the patient must also have at least four of eight symptom criteria in order to be diagnosed with CFS. Fewer than four symptom criteria results in a category termed idiopathic chronic fatigue. With the 1994 definition there was also a consensus on which tests would be necessary to identify exclusionary illnesses.

Fatigue is a very common symptom (38% in a British study) in community-based studies and is reported in many studies performed in different countries in the Western world.[4] In a Swedish study, the lifetime prevalence of chronic fatigue (defined similarly to neurasthenia) was 33% for women and 21% for men.[5] Whether there is an increase of the feeling of fatigue is not known but an American study from 1960 showed that 9% of out-patients report fatigue as a major complaint, while 30 years later 33% of patients at two medical clinics reported fatigue.[6] In order to measure fatigue, standardised instruments should be used and this is recommended for future research.

Table I. Diagnosis of chronic fatigue syndrome (CFS)[3]

Main criteria:
Severe fatigue that persists or relapses for >6 months
Medical explanations are excluded
Classify as CFS if fatigue is sufficiently severe, of new or definite onset, not alleviated by rest, and results in substantial reduction in previous levels of activities and if four or more of the following symptoms exist:
Impaired memory or concentration capacity
Recurrent sore throat
Tender cervical or axillary lymph nodes
Mild muscle pain
Arthralgia
New types of headache
Sleep that is not refreshing
Post-exertional malaise
Classify as idiopathic chronic fatigue if fatigue severity or symptom criteria for CFS are not met

Studies using the 1994 revised CFS CDC criteria based on community populations give a prevalence of the syndrome of 0.1–0.7%, while prevalence in primary care populations ranged from 0.04 to 2.6%. A random digit dialling study including more than 28 000 individuals gave a prevalence of 0.42%.[7] This study latter showed that the syndrome is more common in women, minority groups, and persons with lower levels of education and occupational status.

1.1 Chronic Fatigue Syndrome and Psychiatric Disorders

As patients with nonpsychotic psychiatric disorders share some symptoms with CFS patients including fatigue, cognitive dysfunction and sleep disturbance, and no laboratory-based objective diagnostic test exists, some physicians believe that CFS is a psychiatric disorder. It is recommended that researchers separate patients with psychiatric

comorbidity from those without but who fulfil the CFS criteria to be sure that the data do not reflect the psychiatric disorders.

However, there are findings that distinguish between CFS and psychiatric conditions. One important distinction between major depression and CFS is that guilt, lack of self-esteem and self-blame are rare in patients with CFS.[8] Also, results from patients with CFS differ from those with major depression when comparing the subscales of the results on an instrument used to measure self-reported functional status, the Medical Outcomes Survey 36-Item Short-Form Health Survey (SF-36). Compared with patients with major depression, patients with CFS showed greater impairment in physical functioning, role limitations due to physical health problems, bodily pain, general health perception, vitality and social functioning, and significantly higher scores for mental health and role limitations due to emotional health problems.[9] In addition, there are objective tests differentiating between CFS and depression. The up-regulation of the hypothalamic-pituitary-adrenal (HPA) axis, which is often present in patients with major depression, was not found in patients with CFS who had a down-regulation of this axis leading to low levels of cortisol.[10] Finally, patients with CFS had opposite results to patients with major depression in prolactin release after central stimulation.[11-13]

1.2 Prognosis

Since the internationally accepted definition was established 1994 few follow-up studies have been performed using this definition. However, a systematic review has been completed of studies performed[14] and <10% of patients recover completely. Risk factors for poor prognosis seem to be older age, having a comorbid disorder such as depression and holding a belief that the illness is due to physical causes.

2. Pathogenesis

2.1 The Role of Infectious Agents

Many patients refer to an infectious-like onset and as knowledge about microorganisms started to increase at the end of last century attributions to these have been plentiful. In the beginning of this century several authors pointed out that neurasthenia could follow after several infections, for example influenza virus, *Brucella bovis* and *Toxoplasma gondii*. Since then, different microorganisms have been considered to be involved in the onset of CFS, such as influenza and Epstein-Barr virus (EBV).[15] Fatigue following acute febrile illnesses in soldiers has been reported.[16]

Outbreaks of what retrospectively can be categorised as CFS have occurred,[17,18] for example as in 1948 in the village of Akureyri on Iceland. Other described outbreaks have occurred in hospitals, for example in Los Angeles County hospital in 1934 and in the Royal Free hospital in London in 1955. One of the latest described outbreaks is the Lake Tahoe outbreak in late 1980s.[19] These data together with clinical symptoms and immunological findings have made it plausible that an infectious agent is involved at the onset and possibly throughout the illness.

Viral candidates of most interest have been the herpesvirus family including EBV, cytomegalovirus (CMV), human herpesvirus (HHV) type 6 (HHV-6), HHV-7 and varicella zoster virus (VZV). However, with the exception of HHV-6,[20,21] it has not been shown that there is an active, ongoing infection with any of these viruses[22-30] nor with retrovirus[31] and Borna Disease virus (BDV).[32] The unusual serological responses reported may reflect an epiphenomena associated with a broader immunological impairment. BDV is a neurotropic, negative-stranded RNA, newly classified virus that infects warm-blooded animals to cause profound neurological abnormalities.[32,33] The infection results in a meningoencephalitis with neurological symptoms or in a mild persistent infection with a cognitive affection. Whether BDV naturally infects humans to cause neuropsychiatric disease

remains controversial, however, there are now reports suggesting an involvement of BDV in CFS.[34,35] In contrast, this has not been what others have found[36,37] and the existence of a correlation remains to be proven.

Although the findings do not support a role for ongoing EBV infection in CFS, they do not exclude the possibility that a primary EBV infection can be a triggering event. Six months after glandular fever there is a relative risk of 2.7–5.1 for CFS compared with chronic fatigue following any upper respiratory tract infection.[38]

Another type of virus that has drawn a lot of attention is the enterovirus group[39-41] as clinical symptoms in CFS are similar to those found in enteroviral infections. However, there is so far no clear evidence for an active involvement[42-45] either in serological findings or in studies using muscle biopsies.

This does not exclude a role for CNS trophic viral infections such as enterovirus or HHV-6 acting as an initiator of a process leading to CFS. It is known that viral infections in animal models,[46,47] as well as in humans,[48-50] can affect the HPA-axis, and so infectious agents as a cause of disturbances in CNS function become of particular interest. Dysfunction of the hypothalamus could explain many of the symptoms of CFS.

Borrelia burgdorferi has been seen as a triggering event in some patients but efforts to define persistent infection have failed to yield credible results.[51]

In addition, there is the possibility of an intermittent reactivation of an infection such as EBV or HHV6.[20,23,24,52] However, to date this has not been shown. A possible explanation for the lack of convincing data of a single pathogen that is intermittently expressed may lay in the methods used thus far, which rely on cross sectional study populations, as longitudinal studies are rarely performed.

The involvement of mycoplasma in the pathogenesis of CFS has been discussed. A polymerase chain reaction (PCR) detecting a highly conserved region of the genus mycoplasma detected the organism in peripheral blood mononuclear cells in 52% of patients with CFS and 15% of healthy controls.[53] Confirmatory studies have not been published as yet. An absence of antibodies to *Mycoplasma fermentans* in patients with CFS was noted.[54]

Chlamydia are also agents suggested as possible pathogens in CFS. One study found no association between chronic *Chlamydia pneumoniae* infection and CFS.[55]

Thus, there is evidence that some infectious agents may trigger the onset of CFS, through unknown pathogenic mechanisms. EBV and *B. burgdorfei* are most commonly cited, and both are polyclonal immunologic activators, supporting an immune mediated triggering event as one possible hypothesis. However, evidence for a persistent chronic infectious process is scant, and limited to two agents, HHV-6 and possibly *Mycoplasma* spp.

2.2 Non Infectious Mediators

2.2.1 Sleep

A difference in sleep disturbance between patients with CFS, patients with multiple sclerosis (MS) and healthy controls has been reported.[56] Moldofsky[57] reported similar disordered sleep physiology (an alpha rhythm disturbance within the non-rapid eye movement sleep) in patients with fibromyalgia and CFS. Using the Oxford criteria for the diagnosis of CFS, another study showed disturbances in sleep initiation and sleep maintenance in patients with CFS compared with healthy controls.[58]

2.2.2 Neuroendocrine and Stress Response

The involvement of stress in the pathogenesis of this illness seems clear for most physicians and also many patients acknowledge the influence of this factor on the natural course of symptoms.

At low levels, stress may actually improve some aspects of immune function. However, most types of stress have been shown to impair the function of the immune system and in general the immune defence against viral illness is impaired by stress.[59]

Stress has been proven to be associated with the occurrence of virus.[60] One example is herpes sim-

plex, which rests latent in the neurones and is reactivated by a variety of factors including immune suppression, fever, hormonal changes, and other types of physical and emotional stress.

It has been pointed out that in what today is the most well studied part of our common system of activation, the HPA axis, there must exist a regulation-contraregulation. If there is a stimuli from hypothalamus stimulating the pituitary gland to secrete adrenocorticotrophic hormone (ACTH) which in turn stimulates the adrenal cortex to secrete large amounts of cortisol into the blood, this causes a direct inhibition of the secretion in the hypothalamus of corticotrophic releasing factor (CRF) in healthy volunteers. In conditions of chronic stress different disturbances in this contraregulation can occur.

In patients with CFS the system seems to be exhausted and CRF activity is blunted, and in turn ACTH and cortisol production are reduced. Cortisol levels in both blood[10] and urine[61] have been demonstrated to be low. Using imaging studies, Scott et al. demonstrated reduced adrenal mass in patients with CFS compared with control groups of patients with depression.[62] An hypothesis of a decreased dopaminergic tone in CFS was supported by findings of impairment of growth hormone (GH) response during insulin-induced hypoglycaemia and low nocturnal GH secretion in CFS patients with increase of prolactin and thyroid stimulating hormone levels.[63] Kavelaars et al. suggested CFS should be viewed as a disease of deficient neuroendocrine-immune communication.[64] This area of research is active and results of more studies will probably reveal more about this close communication.

As an example of the effects of a single stress factor, the effects of Hurricane Andrew were studied in patients with CFS in Florida, USA. It was found that patients from the high impact area showed significant increases in physician-related clinical relapses, and exacerbations in frequency and severity of several categories of self-reported CFS physical symptoms compared with patients from the less impact area. Illness burden also showed a significant increase. The post-hurricane distress response of the patient was the single strongest predictor of the likelihood and severity of relapse and functional impairment. In addition, optimism and social support were significantly associated with lower illness burden after the hurricane.[65] Levels of proinflammatory cytokines increased and correlated with symptom severity.

We know today that there is a common chemical language for the brain, immune and endocrine systems, which is partly deciphered.[66] The immune and neuroendocrine systems represent a totally integrated information circuit, a result of sharing ligands and their receptors. The immune system communicates with the neuroendocrine system and can at a local level itself act as an effective endocrine organ. It is likely that small perturbations in immunological stimuli may cause major fluctuations in endocrine status.[67]

2.2.3 Neuroimaging

In order to obtain objective findings of diagnostic value, studies using magnetic resonance imaging (MRI) have been performed. Changes in the white matter considered specific for CFS have been described but not confirmed.[68] So far, no abnormality on MRI has been clearly found in patients with CFS. As white matter changes are seen in an elderly healthy population as well as in other disorders, such as vascular disorders, some dementias and depression, it is important to also have control groups from these patient groups.[69]

In addition, when functional neuroimaging is used the results so far have not been consistent. Again, studies have emphasised a search for diagnostic markers rather than correlations between cerebral blood flow and clinical findings. As the patients experience an impaired cognitive function activation, studies using cognitively demanding tasks should be important. When patients with major depression have been used as a control group, no consistent differences have been found.[69] Hypoperfusion of the brainstem has been reported[70] but technical objections to the evaluation of findings have been made.[68] As a normal range using these techniques has yet to be established,

their clinical utility in CFS research or diagnosis is problematic. As findings using these techniques in a normal population, as well as in other patient groups having impairment of cognitive functions, is to a large extent so far unknown, the optimal use of these techniques in patients with CFS is unknown.

There is preliminary evidence of subtle pathophysiological changes in the brains of patients with CFS and a tendency to enlargement of lateral ventricular volumes.[71] In addition, the presence of brain abnormalities are significantly related to subjective reports of impairment of physical function.[72] Positron emission tomography (PET) analyses have recently indicated that levels of biosynthesis of glutamate, aspartate and γ-aminobutyric acid (GABA) through acetylcarnitine might be reduced in certain areas of the brain in patients with CFS.[73]

2.2.4 Neurocognitive

Neuropsychological testing has been used to try to find objective measurements of the cognitive debilitation found in this condition. In these types of studies it is important to have a well characterised patient group as well as well defined control groups. It is important to also include depressed patients, diagnosed according to criteria in DSM-IV (Diagnostic and Statistical Manual of Mental Disorders [4th edition]), as cognitive deficits are often attributed to depression; a condition commonly found among patients with CFS.[74]

Findings have pointed to a specific type of cognitive deficit found in patients with CFS as impairment of information processing.[75] Impairments in learning and memory were described in a subset of patients.[76,77] When this patient group was compared with patients with MS and patients with depression differences were found in specific tests as in complex auditory information processing where the deficits were greater in CFS patients.[78] DeLuca and coauthors concluded that impaired cognition in CFS cannot be explained solely by the presence of a psychiatric condition.[68] When patients with CFS were divided into subgroups according to those reporting sudden versus those with gradual onset, a differentiation between groups was shown. The rate of concurrent psychiatric disease was significantly greater in the CFS-gradual group compared with the group with sudden onset. While both CFS groups showed a significant reduction in information processing ability compared with controls, impairment in memory was more severe in the patients with sudden onset pointing to a need for stratifying patients according to the type of onset.[79] Although the methodology used can be discussed, some consistent findings have been shown in patients with CFS as impairments of complex information processing speed and efficiency.[80,81]

2.2.5 Immune Studies: Cell Numbers, Cell Function and Cytokine Expression

Early studies suggesting immune abnormalities sparked an interest in an immune-mediated pathogenesis of CFS and an interest in potential immune-based therapies.

Extensive immunological testing has taken place. Changes in the case definition from 1988 to 1994 make comparisons across studies difficult. Nevertheless, none of the abnormalities shown has been proven to be a marker for CFS. A decreased CD4+/CD8+ ratio has been reported as significantly differing from control groups.[52,82] Also, a decrease in CD4+CD45RA+ cells (naive helper T cells) was reported by both these studies, and Straus and coworkers[52] noticed a rise in memory cells (CD8+CD45RO+). Measures of T cell activation have been elevated,[82-84] although not consistently, and elevations in apoptopic markers suggest high cell turn over rates.[85] Otherwise, no significant changes in the number of CD3+ cells or B cells have been found.

Data concerning numbers of natural killer (NK) cells are also contradictory. Some authors report no differences in the number of cells,[23,52] whereas others report lower numbers of NK cells in patients[84,86,87] and others again an increased number,[82,88-90] although the differences are explained for the most part by differences in defining the NK cell population (e.g. CD56+ cells vs CD3-CD8-CD56+).

The NK cell function has been reported to be depressed.[82,87,91] T-cell function is depressed, as demonstrated by T-cell responses to mitogens, and specific antigens are more consistent in that they are depressed[52,82,86,92] and by a depressed delayed-type hypersensitivity reaction.[92]

It is possible that cytokines are a link between a possible infectious agent and symptoms of the CNS. Treatment with cytokines, such as interleukin (IL)-1 can cause similar symptoms as those seen in patients with CFS. Extensive studies, mainly looking for cytokines in serum, have, however, not been conclusive. Bennett et al. showed increased levels of transforming growth factor (TGF)-β in serum from patients with CFS compared with healthy controls and other patient groups.[93] The increased level of this cytokine has earlier been described by Chao et al.,[88] who also described an increase of neopterin, a marker of activation of macrophages. Increased serum levels of IL-6 and IL-1α have also been reported.[94,95] When peripheral cells from patients were cultivated and spontaneous or stimulated release of cytokines measured in a recent study, increased spontaneous release of tumour necrosis factor (TNF)-α and Il-6 were seen, while spontaneous as well as stimulated release of IL-10 was suppressed.[96] In symptomatic CFS patients, this is not seen during relative periods of wellness and not induced by exercise.[96]

Female patients commonly report increased symptom severity correlating to the menstrual cycle. Cannon and coworkers showed an abnormality in IL-1β secretion in patients that may be related to altered sensitivity to estradiol and progesterone.[97] They also show increased release of IL-1R antagonist and soluble IL-1R type II by cells from patients suggesting a chronic, low-level activation of the immune system.

Another marker for activation of the immune system is the upregulation of the 2-5A synthetase/RNaseL antiviral pathway, an enzyme produced in leucocytes and induced by interferon found in patients with CFS.[98,99] It leads to increased RNase levels and decreased cell metabolism.

2.2.6 Link Between Immune Findings and States of Chronic Infection/Autoimmunity

Thus, the key immune findings in patients with CFS are: (i) chronic immune activation; (ii) a cytokine shift to proinflammatory cytokine expression and Th2 cytokine expression; and (iii) abnormalities of cell function, particularly the NK cell function.

Chronic immune activation should result from chronic antigenic exposure to either foreign antigens (e.g. chronic viral infection) or self-antigens (e.g. autoimmunity). The cytokine imbalance seen in patients with CFS also suggests a chronic state of either autoimmunity, with a Th2/proinflammatory cytokine pattern, or vulnerability to chronic viral infection, with suppression of Th1 cytokines and expression of proinflammatory cytokines. Poor nonspecific immunity (poor NK cell function) would also increase vulnerability to chronic viral reactivation. While the existing data thus far leans towards chronic viral reactivation in this particular setting, it is possible that two immunological subgroups may coexist under the umbrella diagnosis of CFS.

2.2.7 Neurological Versus Immune Interaction

Whether the immune abnormalities seen in patients with CFS could entirely result from the neurological and neuroendocrine abnormalities also seen in this illness is unclear, just as the hypothesis suggesting the neurological and neuroendocrine defects result from the cytokine imbalance and chronic immune activation seen in CFS is also unclear. It is interesting that the blunted HPA axis results in low cortisol expression in patients with CFS and cortisol would normally function to help down regulate T-cell activation. Similarly, the observation that proinflammatory cytokines directly disrupt the sleep cycle in animal models, and thus would disrupt normal circadian rhythm and blunt the HPA axis is a postulate difficult to test in established ill populations.[100]

2.2.8 Stress Response

Studies in the field of psychoneuroimmunology have shown that stress can induce modulation of the immune system through the HPA axis and the sympathetic-adrenal medullary (SAM) axis.[101,102] The consequences on health have been reviewed[103] and stress response models have been discussed, both in the development of the illness and as a potential mediator of the persistence of the illness.[59] While the former is hypothetical, with little prospective data, the latter is an area of active investigation. At issue is whether the normal stress response, with its neuroendocrine and immune consequences, is playing a role in illness persistence. There is considerable data in other chronic illnesses, such as coronary artery disease, diabetes mellitus and HIV infection, to suggest that coping strategies to common life stressors can impact the severity of illness and outcome.

Studies in a CFS cohort after a major life stressor demonstrated both immune and health consequence to the stressor (Hurricane Andrew) were modified by either healthy or maladaptive coping strategies.[65] Intervention studies to modify coping skills have been a major focus in the treatment of this chronic disabling illness as described under section 3.3 on cognitive behavioural therapy (CBT).

3. Treatment

In general, studies performed so far provide insufficient data for a conclusive treatment recommendation.[104] The unravelling of the aetiopathogenic mechanisms of CFS is an essential prerequisite for fatigue pharmacotherapy. The following subsections summarise the literature on clinical interventions.

3.1 Pathogenesis-Driven

A study investigating the use of antiviral therapy (aciclovir) compared with placebo[105] resulted in adverse effects of therapy and no benefits. However, aciclovir has little efficacy against herpes viruses that do not entirely rely on thymidine kinase (e.g. EBV, CMV, HHV-6 and HHV-7).

Immuno-modulatory studies performed thus far provide insufficient evidence for conclusions. One trial with intravenous γ-globulin 2g/kg bodyweight over 3 months resulted in improved general health (symptoms and functional capacity),[106] but no change in quality of life and depression scores. The Australian group were unable to confirm these initial findings in a repeat study.[107] In another study using γ-globulin 1g/kg over 6 months, only social functioning improved favouring placebo.[108]

Interferon (IFN)-α-2a was compared with placebo, with no improvement of quality of life or clinical well-being shown.[109] Another study, randomised but not double-blind, used IFNα-2b.[110] Five of 19 patients improved and three recovered completely. The small numbers of patients in these trials means that larger confirmatory studies are required before IFNα can be considered for clinical use.

Transfer factor therapy (extract from donor lymphocytes) has been tried without success,[111] although the trial was hampered by a small study sample.

In a study using staphylococcus toxoid vaccine, patients with CFS also diagnosed with fibromyalgia showed clinical improvement but did not improve in neurocognitive function and sleep problems, depression or pain.[112] One trial using mismatched double-stranded RNA, which has immunomodulatory as well as antiviral effects, improved health, physical functioning, activity level and cognition in a placebo-controlled trial in patients with CSF.[113] A phase III clinical trial of continuous long-term therapy is underway.

Two phase I studies attempting to down regulate proinfammatory cytokines have been reported with suggestions of potential for clinical efficacy, although placebo control trials are not yet underway.[114]

3.1.1 HPA Axis Dysfunction

Two short-term, placebo-controlled trials using low-dose glucocorticoids (hydrocortisone) showed some improvement of fatigue or sense of wellness but had a moderate risk of suppressing the function of the adrenal glands. One was a 12-week study[115]

and one a 4-week-study.[116] Two studies using low-dose (fludrocortisone 0.1mg) mineralocorticoids[117,118] for an associated condition, neurally mediated hypotension, showed no benefit.

GH levels have been demonstrated to be blunted in patients with CFS. GH therapy was compared with placebo for 3 months and quality of life was not improved.[119]

3.1.2 Others

An anticholinergic inhibitor (galantamine) resulted in significant improvements for sleep and myalgia compared with placebo.[120] However, a multicentre study set up with this drug was recently interrupted as no benefits were shown and adverse effects were noted.

Nadide (nicotinamide adenine dinucleotide) treatment for 4 weeks showed improvement of symptoms in 31% of patients compared with 8% in the placebo control group. Confirmatory studies have not been published.[121]

3.1.3 Sleep

No specific sleep studies utilising CFS populations have been undertaken. It is common practice to use medications known to benefit fibromyalgia patients in patients with CFS (e.g. tricyclic antidepressants), although CFS focus studies have not examined these medications for benefit or risk.

3.2 Symptom-Based Therapies

Therapies that aim to treat CFS symptoms, such as allergy, depression and exercise, have also been investigated.

Antihistamines have been tried (terfenadine) and compared with placebo with no therapeutic benefits found.[122]

Placebo-controlled trials have evaluated antidepressant therapy (phenelzine, fluoxetine, and two monoamine oxidase inhibitors [selegiline and moclobemide]) and no improvements have been reported.[123-127]

One study compared graded aerobic exercise to flexibility/relaxation training. Those having exercise felt significantly more improved and better in terms of fatigue, functional capacity and fitness.[128] Another study compared an antidepressant with exercise to exercise with drug placebo, or antidepressant with exercise placebo. Fluoxetine, the antidepressant had an effect on depression and exercise significantly improved health perception and fatigue at 28 weeks.[125]

In a study of massage therapy, a significant improvement on depression, anxiety, fatigue, sleep, severity of symptoms and pain was shown.[129]

Magnesium therapy given as weekly injections produced an improvement in overall health and emotional reactions.[130] However, no confirmatory studies have been published.

Essential fatty acid therapy was given in one study[131] and no significant improvement was noted for the patients. A placebo-controlled study be Behan et al. showed efficacy with evening primrose oil.[132]

Liver extract has been compared with placebo but no significant differences were found between treatment and placebo groups.[133]

3.3 Cognitive Behavioural Therapy

Cognitive behavioural therapy (CBT) has been used in different schemes either in groups[134] or, more successfully, on an individual basis.[135,136] The latter form proved highly efficient at 1-year follow-up. A 5-year follow up of CBT shows that it can produce some lasting benefits but is not a cure.[137] Recently, a Dutch study showed that CBT was more effective than guided support groups and the natural course of the syndrome in a multicentre trial with many therapists.[138] A lower proportion of patients improved than when CBT was given by a few highly skilled therapists. A finding was that the support group had worse prognosis than the group where the natural course was followed.

3.4 General Aspects on Treatment

An evaluation by patients with CSF of medical treatment showed that satisfaction with healthcare received was in general low.[139] The complaints included insufficient information and emotional support from their doctors forcing the patients into

alternative and often expensive treatments. Most physicians coming into contact with CFS describe this patient concern. The clinician knowledge base on CFS is limited, with 85% of cases confirmed in a large CDC prevalence study previously undiagnosed.[140] Without clear clinical guidelines, clinical management of patients with CFS is not developed at all levels of the healthcare system. It causes problems for many clinicians.[141] Clinician education is urgently needed and effective management strategies disseminated to the medical community.

The stress of having a chronic illness can impact the outcome of any patient, and the stress of having little faith in the physician's knowledge and ability to help manage this difficult illness certainly compromises the patient's hope for clinical improvement. A deepened understanding of a well functioning doctor-patient relationship is needed.

In evaluating a patient with suspected CFS, a thorough clinical investigation excluding other explanations is of the utmost importance both for the doctor and the patient. A complete detailed life history is important, including not only the medical but also the psychological history and, especially, potential traumas. Exclusion of psychiatric problems demanding psychiatric or psychological expertise is crucial. Exclusionary or comorbid sleep disorders should also be carefully evaluated and treated.

If the diagnosis of CFS is established, the patient should receive information on the current knowledge of CFS and this should be updated as advances in the field appear.

CBT on an individual basis should be used if possible. A consistent pattern of living with work, rest, sleep and physical activity should be applied and a slow increase of daily activities introduced. It should be explained that even a slow increase in physical exercise could cause an exacerbation of symptoms at the start, but that they subside with time and there is an overall improvement. Use of medications for the associated symptoms of CFS should be used with caution. CFS patients are often drug intolerant and adverse effects are common.

Consensus guidelines for the management of patients with CFS are being developed in the UK, Canada and Australia, and should be published in the near future.

4. Conclusion

The dichotomy introduced by Platon of the perception of humans as consisting of a body and a soul, and reinforced by philosophers such as Descartes in the early 1600s, has given our culture an outlook of its own on the concept of health, a separation of mind and body. Experiencing an illness where no objective marker exists is looked upon differently to experiencing a disease in which objective measurements of a pathological process can be performed. When an illness is not yet clearly biologically defined, the care given to individuals experiencing this illness is often poor in today's medical environment. There has been a split in the literature to 'claim' CFS as an illness of the mind or an illness of the body. Yet the data clearly demonstrate the involvement of both systems, in an interactive fashion.

CFS can be seen as a model of 'unhealth'. In this model, the biological derangement leads to symptoms that our culture considers either as psychosomatic or as imaginative. Current research points to an intimate relationship between the immune system and the central nervous system with the possible involvement of a microorganism, at least at the time of onset, causing disturbances magnified in systems affecting the function of the individual. The pathogenesis is bound to be complex and it may well be that the solution will come together with an altered outlook on the concept of illness.

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