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CHRONIC FATIGUE SYNDROME*

A. Chaudhuri, Wilhelmina M.H. Behan and P.O. Behan, Southern General Hospital, Glasgow and Western Infirmary, Glasgow‡

Chronic fatigue syndrome (CFS) is a disabling illness characterised by persistent and overwhelming fatigue. For clinical and epidemiological purposes, CFS is defined according to the modified Centres for Disease Control (CDC) criteria which were developed by the International CFS Study Group in December, 1994.[1] The hallmark of this disorder is an overwhelming sense of tiredness, lack of energy and feeling of exhaustion, and is distinguishable from the peripheral fatigue which reduces maximum force output.[2] The fatigue can come on suddenly or gradually, and persists throughout the period of illness; patients are thus forced to function at a level of activity which is substantially lower than their usual capacity. Patients also generally report a wide range of symptoms such as generalised muscle aches and pains (fibromyalgia), weakness, sleep disorder, impaired concentration and memory,[3] and often suffer from atopies and recurrent infections. In this review, we present the current state of knowledge on CFS and suggest a possible pathogenesis.

EPIDEMIOLOGY

The prevalence rate of CFS in the United States is estimated as between 4-10 cases per 100,000 adults of 18 years and above.[4] The prevalence of self-reported and idiopathic chronic fatigue may be several fold higher.[4] In the United Kingdom, a recent report[5] of the joint committees of the Royal Colleges of Physicians, Psychiatrists and General Practitioners estimated the population prevalence of CFS in primary care to be 0.1-0.9% based on the restrictive CDC criteria (excluding patients with psychiatric disorder), and 1.5-3% using the broader Oxford criteria, but these are considered to underestimate its true prevalence.[6]

In adolescents, the rate is slightly lower than that in adults; cases in children of less than seven years are very rare.[3] Most cases occur sporadically, although the disorder was originally recognised in an epidemic setting. Women are affected more often than men, and most patients are in the age range of 25-45 years.

CLINICAL PRESENTATION

Onset and precipitating factors

In approximately one-third of CFS cases the onset is abrupt and subacute; it is insidious in the remaining two-thirds.[7] Nearly 80% cases of CFS follow a respiratory, gastrointestinal or other acute infection with 'flu-like symptoms'.[8] The epidemic form of CFS was calculated to have an incubation period of five days (range 4-10 days).[9] CFS may also develop after emotional or physical trauma,[4,7] immunisation,[3] ciguatera fish poisoning,[10] or food botulism.[11] We have recently described a neurobehavioural syndrome identical to CFS associated with chronic exposure to low-

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†Correspondence to Professor PO Behan, Department of Neurology, Southern General Hospital.

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dose organophosphate pesticides:[7,12] it is possible that other environmental agents or toxins might serve as triggers of this disease. CFS may also occur in association with the sick building syndrome,[13] after a prolonged period of stress,[14] severe physical exercise,[15,16] multiple chemical sensitivity,[17] and has been linked to silicone breast implants in women.[18,19]

There may be more than one precipitating factor and co-existing disorders such as Gilbert's disease, atopy or endometriosis may play a role in increasing host susceptibility to the development of CFS.[7] A significant proportion of CFS patients attending our clinic have asthma, eczema, atopy or serologic evidence of coeliac disease; the latter association may be important since cryptic gluten sensitivity may play a role in neurologic diseases.[20] A number of male patients have developed CFS following an episode of epididymo-orchitis.[3] A recent study of Persian Gulf War veterans has now concluded that the symptoms are identical to CFS and to fibromyalgia.[21]

Physical symptoms

Fatigue remains the most important and the central symptom in CFS. It must fulfil the characteristics as defined in the CDC criteria, i.e. fatigue has to be of definite or new onset and not the result of on-going exertion, to be generally unrefreshed by rest and sleep, and results in substantial reduction in overall performance for a consecutive period of six months or longer. Other symptoms in CFS are listed in Table 1. A patient must fulfil at least four of the first eight symptoms to qualify for CDC-defined CFS.

TABLE 1
Chronic fatigue syndrome - symptoms other than fatigue.

- Impaired short-term memory or concentration
- Sore throat
- Tender cervical or axillary lymph nodes
- Muscle pain
- Headaches of new type, pattern or severity
- Unrefreshing sleep
- Post-exertional malaise lasting >24 hours
- Multi-joint pain without joint swelling or redness
- Others: chest pain, sweating, vertigo or dysequilibrium, photophobia, transient visual obscurations, irritable bowel syndrome, idiopathic cyclic oedema, prostatism or menstrual disorders

Paroxysmal attacks of chest pain and sweating are two other symptoms commonly found in this condition. Indeed, many patients with CFS were originally referred to us by cardiologists as having syndrome X (anginal chest pain with normal coronary arteries). Unexplained attacks of severe sweating, typically nocturnal, are common.

Of the neuropsychiatric findings, the most consistent is mild, atypical depression. Well-characterised cases invariably report cognitive deficits, usually anomia, impaired short-term memory and concentration difficulties. Some patients develop hypergraphia, i.e. keeping detailed records and long descriptions of all their symptoms, and come to the clinic with interminable notes. However, patients never have anhedonia or the suicidal symptoms of typical depressive illness although a pre-morbid psychiatric abnormality ('depression-prone') may be evident.[22]

Factors that improve or worsen fatigue

Pregnancy is the only time when women experience significant improvement of their symptoms but there is often severe 'rebound fatigue' in the early puerperium.[3] A variety of specific and non-specific factors appear to make the fatigue and other associated symptoms worse, including a heavy meal, a prolonged hot bath or alcohol.[3] Some patients get such a distressing reaction to the smallest amount of alcohol ingested that they abstain entirely. Both physical and mental efforts can worsen fatigue in CFS.[3]

There is an exacerbation of both physical and mental symptoms during menstruation: with worsening of fatigue and myalgia, and women 'whose menstrual phase had not been previously marked by hyperirritability and emotional tension complained that they could not control themselves and flew into rages at what they realised were really insignificant frustrations or annoyances'.[23]

Clinical signs

Despite a wide variety of symptoms, few patients with CFS have objective clinical signs at the time of examination. 'Soft' neurological signs may occasionally be detected, such as postural hand tremors and focal myokymia ('benign fasciculations'). Patients with dysequilibrium symptoms ('Pedersen's syndrome') are unable to walk in tandem but otherwise cerebellar signs are absent. Though a number of patients have intermittent symptoms of hemi-sensory pain or dysaesthesia (hemi-sensory syndrome), objective sensory loss is rarely documented. Rarely, patients develop Parkinsonian features of facial rigidity, hypokinesia and slow gait.

Patients with CFS are not permanently wheelchair-bound. Patients in wheelchairs without other disease, who have been diagnosed as having CFS, on detailed scrutiny turn out to have a primary personality disorder; these are typically young women characterised by avoidance of social interaction and craving for assistance, even for toilet care and feeding. They prefer to be alone in their own rooms with the curtains drawn, avoiding any contact with bright light because of photophobia. We call this 'Miss Haversham syndrome'.*

DIFFERENTIAL DIAGNOSIS

When fatigue is combined with myalgia a long list of differential diagnoses can be generated (Table 2) which must be excluded by appropriate tests before a diagnosis of CFS is made. In practice, perhaps the most important differential diagnosis of CFS is depression. Depressed patients commonly complain of fatigue. However, depressive features not present in CFS are (1) recurrent thoughts of death or suicidal ideation; (2) markedly diminished interest or pleasure in all, or almost all daily activities (anhedonia); (3) excessive or inappropriate guilt. Hallucinations and delusions are not a feature of CFS. There is an overlap of CFS symptoms and somatisation disorder,[24] in which the physical complaints begin before the age of 30 years and generally have been present for five years or more. In contrast, CFS is usually diagnosed within a year or two of the onset. The conversion disorder can present with lethargy and non-localisable neurologic symptoms, but there is no abnormality on physical examination. The majority of CFS patients have no evidence of hyperventilation either at rest or in response to the physiological provocations of exercise and voluntary over-breathing.[25] Chronic hyperventilating patients also have agoraphobia, a symptom which is not recognised in CFS patients.[26] Because of the abundance of information currently available about CFS in the lay media, the Munchausen phenomenon, i.e. a fictitious shamming of the syndrome, may occur with patients purporting to suffer from CFS.

*Referring to the well-known Charles Dickens character.

TABLE 2
Other disorders associated with chronic fatigue syndrome.

Anaemia	(all causes)
Autoimmune diseases	(Sjögren's syndrome, polymyositis)
Drug-induced conditions	(alcohol, sedatives, interferon, HMG-CoA-inhibitors)
Endocrine disorders	(hypothyroidism, hyperparathyroidism, Addison's disease, polyglandular insufficiency)
Metabolic disorders	(haemochromatosis, metabolic myopathies)
Malignancy & Paraneoplastic syndromes	(limbic encephalitis)
Neurological diseases	(multiple sclerosis, demyelinating neuropathies, Parkinson's disease, multiple system atrophy)
Obesity	
Sarcoidosis	
Sleep disorders	(narcolepsy, obesity-hypoventilation syndrome)
Systemic infection	(viral, bacterial, fungal, parasitic or protozoal)
Vasculitides	(SLE, giant cell arteritis, Wegener's granulomatosis)
Withdrawal syndromes	

Post-polio fatigue

Fatigue is the most commonly reported, most debilitating post-polio sequel affecting 1.63 million polio survivors in America alone.[27] Its features are similar to those of CFS. Autopsy studies performed more than 50 years ago revealed frequent, severe lesions in the reticular activating system (RAS) in post-polio patients.[28,29] Like fatigue, hypotension is common to both CFS and post-polio cases, possibly due to dysfunction of the brain stem and hypothalamus.[30]

LABORATORY FINDINGS

Routine laboratory tests seldom reveal any specific abnormality in the chronic phase of the illness though some do occur more often than by chance (Table 3).

Immunology

Non-specific immunological abnormalities have been widely reported in this condition. Tests for heterophile antibody was found to be positive in an average of 15% patients in pooled data.[31] No difference has been recorded in the serology testing for Lyme disease (*B. burgdorferi* antibodies) between patients and controls.[15] There is also incontrovertible evidence that CFS patients suffer from atopy more frequently than normal population for which an aberrant cytokine response is a possible explanation.

Virology

It was suggested that CFS could be an acquired metabolic myopathy induced by persistent virus infection.[32] Early investigation linked EBV (the causative agent for infectious mononucleosis) and CFS - the so-called chronic mononucleosis syndrome [33,34] - but subsequent studies have failed to substantiate this.[35,36] Persistence of enteroviruses was considered to be an attractive hypothesis for fatigue, myalgia and non-specific muscle abnormalities.

TABLE 3
Abnormal laboratory findings in CFS.[31]

Haematology:	Leucopenia, relative lymphocytosis, monocytosis (~30%) Raised ESR (~15%) Reduced serum folate (~10%) Abnormal RBC morphology ('nondiscocytic erythrocytes')
Biochemistry:	Elevated LFT and CK (~5-20%) Reduced intracellular carnitine Elevated levels of serum angiotensin-converting enzyme (ACE) Reduced 24-hour urinary cortisol
Autoantibodies:	Anti-thyroid (microsomal) & anti-gliadin positivity (~10-30%) Low concentrations of antinuclear antibody and Rheumatoid Factor False positive VDRL (~1-8%)
CSF:	Faint oligoclonal bands (~1-2%)
ECG:	Non-specific ST and T wave changes
EEG:	Slowing of background rhythm, usually over temporal regions

in CFS,[37,38] which was further supported by the similarities between CFS and post-polio syndrome. However, enteroviruses and other putative candidates for persistent virus infection, such as human herpes viruses, cytomegalovirus or measles virus have not been identified in current research.[39] Similarly, no evidence exists that CFS is due to persistent retroviral infection, whether caused by HIV or other human T cell lymphotrophic viruses.[31,39]

We carried out experiments to analyse tissue from patients with CFS, affective disorders and normal controls for Borna disease virus (BDV) since there is some circumstantial evidence that BDV can affect the central nervous system of man causing a variety of different psychiatric illness. All samples from healthy and depressed controls were negative, and only two CFS patients proved positive for BDV.[40] While it is clear that infection with any of these agents may result in CFS, and even though viral persistence can be documented in some using molecular cloning techniques, it is not now thought that such persistence is contributory to the genesis of the illness.

Genetic studies

Previous studies have consistently failed to show any specific pattern of HLA-haplotype in CFS patients as compared to control subjects.[3] We postulated that a mitochondrial disorder may underlie the illness because of the mitochondrial proliferation and pleomorphism identified in a series of cases.[41] Several mitochondrial DNA (mtDNA) deletions were reported in a typical case of CFS[42] and we found the common mtDNA[4977] deletion in two of eight cases.[43] Despite the lack of evidence of a genetic basis for CFS, we have seen from time to time, more than one member of the same family being affected by this illness and the process of a subtle genetic predisposition, possibly related to maternal (mitochondrial) inheritance, cannot be totally dismissed.

MUSCLE STUDIES

Biopsies

A variety of non-specific findings have been recorded inconsistently. In about 30% of cases, scattered atrophic fibres are present and in another 30%, there is Type 2 fibre hypertrophy and predominance.[44] Type 2 fibre atrophy was also occasionally noted. Nearly half of the biopsies were entirely normal.[44] Rare cases had evidence of myoadenylate deaminase deficiency; there is no present consensus on the implications of this finding except that it has been reported after a viral infection and in association with myalgia. One ultrastructural study showed mitochondrial changes,[41] but these have not been confirmed.

Bioenergetics[31]

^{31}P nuclear magnetic resonance spectroscopy (NMRS) provides an excellent method for continuous, *in vivo*, monitoring of intracellular energy metabolism in skeletal muscles. NMRS studies have shown a significant reduction in the exercise capacity in CFS, accompanied by excessively early intracellular acidification.[45-48] The first positive report of a single case of CFS[45] was followed by work from the same group showing similar features in five of six cases,[46] and then in 12 out of 46 patients:[47] six had increased acidification relative to phosphocreatine (PCr) depletion and six, reduced acidification. A significant reduction in aerobic metabolism was noted in PCr recovery.[48] Skeletal muscle NMRS studies in syndrome X have reported similar underlying abnormalities, supporting our clinical observation that CFS and syndrome X could have a similar metabolic disorder.[49] Reduced oxidative muscle metabolism in CFS patients has recently been confirmed in another study which compared 22 CFS patients to normal sedentary subjects before, and two days after, a maximal treadmill test.[50] Muscle oxidative capacity was measured as the maximal rate of post-exercise PCr re-synthesis in the calf muscles using ^{31}P NMRS. The oxidative capacity (maximal rate of ATP synthesis) was significantly reduced in CFS patients as opposed to controls. No further changes, however, were seen in the post-exercise period.

Cell culture

Aerobic metabolism was evaluated in myoblast cultures established from muscle biopsies of 16 typical cases of CFS compared to ten normal controls.[51] There was a statistically significant broader range of lactate/pyruvate (L/P) ratios, a measure of the redox function, in the patients' myoblast cultures, compared to controls. Culture from 10 of the 16 cases showed mild defects of aerobic metabolism, with myoblasts from two patients showing increased L/P ratios, suggestive of a defect in oxidative phosphorylation while eight had decreased ratios, consistent with a mild deficiency in pyruvate dehydrogenase. Mitochondrial volume was not significantly increased and no mtDNA rearrangements were present. One of the patients with decreased L/P ratio had biopsy findings suggestive of a mild mitochondrial myopathy.

EXERCISE TESTS

Since, by definition, CFS patients experience profound deterioration of their fatigue and muscle symptoms after exercise, a number of studies have looked at post-exercise motor performance.[52-56] In an incremental treadmill protocol (walking to exhaustion), CFS patients showed a lower VO_2 max (maximum volume of oxygen consumed) as compared with controls in the absence of any cardiopulmonary abnormality.[52] Other studies on exercise performance and fatiguability could not demonstrate any difference

between patients or controls though about a third of CFS cases had an abnormal lactate response and tachycardia.[54] We carried out repetitive isometric quadriceps exercise (knee extension against fixed resistance) in a well-characterised group of CFS patients and compared their performance with matched controls. Whilst there was no significant difference between the groups during the first part of the exercise, a markedly rapid decline in quadriceps tension was evident in the patient group at 200 minutes and on the following day (after 24 hours) during recovery. This is the first objective evidence of post-exercise fatigue in CFS.[57]

OTHER LABORATORY FINDINGS

Nerve conduction studies(NCS) and needle electromyography(EMG)

Several studies have shown that motor and sensory NCS are normal in all cases of CFS. One study showed that in approximately one-third of patients, a reduced recruitment pattern of voluntary motor units with grouping of motor units on maximum voluntary contraction was detected and single fibre EMG(SF-EMG) was abnormal in 75% patients with an increased jitter, but no impulse blocking.[58] However, this observation has not been confirmed.[59] Motor fibre density was found to be normal in CFS patients in SF-EMG studies.

Table tilt testing

An abnormal response to upright table tilt was found in 22 of the 23 patients with CFS as against 4 out of 14 controls.[60] During the first 40 minutes of the upright tilt, symptomatic patients maintained stable heart rate and blood pressure but subsequently, there was an abrupt decrease of both the heart rates and blood pressure, and development of severe presyncopal symptoms (warmth, light-headedness, nausea and sweating). This phenomenon, called neurally-mediated hypotension (NMH), is considered to be due to an abnormal cardiovascular reflex mechanism in CFS patients.

Neuroimaging

Anatomical visualisation of the neuroaxis has always been normal in CFS patients with no specific abnormalities on conventional CT and MRI scans. Regional cerebral hypoperfusion, however, was noted by us and others in the Single Photon Emission Computed Tomographic (SPECT) cerebral-flow scans.[61,62] The hypoperfused areas were cortical and subcortical, typically involving the temporal lobes in our study,[61] while hypoperfusion of the brain stem was reported in another study.[62] No consistent pattern has emerged but it is clear that patients with CFS, both children and adults, may have multiple areas of regional cerebral hypoperfusion.

ROLE OF TOXINS IN CFS

Few studies have addressed the issue of toxins in producing CFS. Chronic, low-dose organophosphate exposure is one of the suggested toxic models of CFS. Organophosphates (and carbamates) are potent inhibitors of neuronal acetylcholinesterase and long-term neurological abnormalities after exposure to these agents are well recognised.[63] Patients who develop CFS after chronic low-dose organophosphate exposure are extremely sensitive to such compounds, and develop catastrophic fatigue and cardiac arrhythmias when exposed even to a minute amount. These agents also affect the immune system and can produce a wide variety of abnormalities. Further evidence for a cholinergic role in CFS patients comes from the observation that the survivors of food-borne botulism during the epidemic of late 1980s in North England and Wales developed symptoms of CFS

over the following years.[11] Botulinum toxin is known to selectively act on the pre-synaptic cholinergic nerve terminals inhibiting the release of synaptic acetylcholine. There was no obvious correlation between the severity of the acute poisoning and the subsequent development of chronic fatigue.

CFS also occurs after ciguatera fish poisoning; the toxin is a potent inactivator of the neuronal sodium channels.[64] Organochlorines have been postulated to have an aetiologic role in CFS and one study documented a higher level of total organochlorine and hexachlorobenzene in patients who developed symptoms of CFS after organochlorine exposure, as opposed to controls.[65] Chronic lead poisoning can have an identical presentation to CFS.[66] Patients with multiple chemical sensitivity (MCS) share symptoms with CFS and are sensitive to a large number of chemicals even in very small doses.[17] The 'supersensitivity' phenomenon that characterises the symptomatic CFS patients who develop the illness after exposure to one or more chemicals is possibly mediated by an olfactory-limbic mechanism.[67]

HYPOTHALAMIC DYSFUNCTION IN CFS

Symptoms that suggest hypothalamic involvement in CFS are (1) fatigue; (2) sleep disorders (somnolence and sleep-rhythm reversal); (3) abnormal sweating; (4) altered temperature; (5) poikilothermia; (6) mood disorder; (7) changes in appetite and craving for certain foods; (8) weight changes and idiopathic cyclic oedema; and (9) menstrual dysfunction. We have reported abnormal hypothalamic arginine-vasopressin secretion and water metabolism in CFS patients,[68] idiopathic cyclic oedema, a condition frequently accompanying CFS in women, is associated with abnormalities in the regulation of gonadal hormones and prolactin, presumably due to hypothalamic dysfunction. In the post-polio fatigue syndrome abnormal prolactin release was documented with a correlation between the prolactin level and the severity of fatigue symptoms.[69,70]

An abnormality of the hypothalamic-pituitary-adrenal (HPA) axis in CFS has been demonstrated;[71] supersensitive cortisol responses to exogenous ACTH suggest a pituitary-deficient hypo-cortisolic state. All patients had normal levels of circulating ACTH but showed an evening rise as compared to normal subjects. The pituitary ACTH release was blunted in response to exogenous CRH, but this is not unique to CFS and is found in various other conditions associated with stress and in the overtrained athlete. Presumably, this reflects a lack of adaptation of the HPA axis to chronic stress which may be a key trigger for the development and perpetuation of CFS. There is also evidence to suggest that CFS patients have a reduced volume of their adrenal glands, which could indicate a hypofunctioning HPA (Professor T.G. Dinan, personal communication); whether this observation is an epiphenomenon or a primary cause of fatigue remains to be elucidated.

NEUROENDOCRINE ABNORMALITIES IN CFS

Neuroendocrine axis assessment has traditionally been considered one of the best and safest approaches for assessing specific neurotransmitter functions in the central nervous system.[72] A variety of abnormalities have been described in the neuroendocrine functions (Table 4) of which the most consistent is the evidence of upregulated serotoninergic activity,[73,74] but supersensitivity to acetylcholine, and reduced sensitivity to norepinephrine, glucocorterids and vasopressin have been claimed.

TABLE 4
Neuroendocrine abnormalities in CFS.

Supersensitivity to:	serotonin (5 HT) acetylcholine
Subsensitivity to:	norepinephrine glucocorticoids (possibly) vasopressin

RECENT RESEARCH

Resting energy expenditure in CFS

Resting energy expenditure (REE) is the energy expended by an awake, alert subject in the post-absorptive state. REE accounts for between 60% and 90% of the total energy expenditure[75] and any increase in REE, in the absence of compensatory increase in diet, should result in there being less energy available for other physical activities. We carried out a study to investigate REE in patients with CFS and healthy controls. REE varies with body size; therefore, several body compartments that are potentially important in the prediction of the expected REE were also measured. These compartments were total body potassium (TBK), total body water, extracellular water and intracellular water. Eleven female patients with CFS were studied together with 11 healthy female control subjects in the same height, weight and age range. Since gross indices of body mass, such as height and weight are relatively poor predictors of the expected REE, TBK was chosen as the predictor of the expected REE.[76] Using TBK as a predictor of the expected REE, we found a significant rise in REE in 5/11 patients as compared to controls. This finding offers one possible contributor to fatigue in some CFS patients in that the energy available for physical activity is being diverted to fulfil the increased energy requirements of the presumably metabolically overactive tissue.

Thallium scans and CFS

Myocarditis, with or without Bornholm disease-type pain was common in an analysis of 1,000 patients with CFS seen in Glasgow over the past 20 years.[3] We were struck by the frequent association of acute chest pain resembling an acute coronary event in the development of CFS. These patients underwent extensive cardiological investigations which were normal but, on subsequent clinical follow-up, had a clinical course which was indistinguishable, from patients who had had a viral infection and went on to develop CFS. A significant number of cases of this so-called syndrome X therefore strongly resemble CFS. Furthermore, nuclear magnetic resonance spectroscopy studies of skeletal muscle in patients with syndrome X show abnormalities identical to those found in patients with CFS.[49]

Cardiac thallium-201 SPECT scans on a series of syndrome X patients revealed abnormalities in a significant proportion;[77] the intravenous injection of radioactive thallium-201 rapidly accumulates intracellularly in a similar fashion to potassium. The abnormalities seen in the scans are not due to coronary stenosis since all these patients have angiographically-normal coronary systems. Waldenström proposed that the defect in the uptake of thallium-201 could be due to a change in cell metabolism resulting from abnormal ion leakage and not to microvascular ischaemia.[78]

We carried out scans on a small group of well characterised CFS patients without any symptoms of chest pain. None of the patients had any cardiac symptoms at the time of their scan but image analysis revealed moderate perfusion defects in the left ventricles of 70% of the patients studied.[79]

TREATMENT

Treatment in CFS has so far been symptomatic, mainly directed to the relief of painful symptoms, sleep problems and the associated mild depression. It is important that concomitant illnesses that might contribute to one or more of these symptoms are excluded before such therapy. Treatment of fatigue in CFS has largely been unsuccessful and no sustained benefit was observed from the use of a number of agents in open-labelled trials. These included corticosteroids, mineralocorticoid (fludrocortisone), amantadine and 3,4 diaminopyridine. No improvement occurred in most of our patients treated with nutritional supplements such as essential fatty acids, coenzyme Q_{10}, carnitine and choline. We also used antiepileptic drugs like carbamazepine, lamotrigine and phenytoin, which are effective for pain relief and suppressing ephaptic neuronal activation that occcurs in neuralgias. Patients treated with carbamazepine did experience a partial reduction of fatigue and so did a few patients on lamotrigine. Except for occasional patients with fibromyalgia and CFS who responded to low-dose amitriptyline, use of antidepressants (both monoamine reuptake inhibitor and selective serotonin reuptake inhibitor [SSRI] groups of drugs) in any dose range, failed to improve the central symptom of fatigue in most patients though overall, patients experienced less frequent mood swings while taking one of the selective SSRIs, sertraline, or one of the newer antidepressants, venlafaxine.

In our experience, there was no sustained improvement of fatigue with the use of central stimulants (nicotine transdermal patches and methylphenidate, alone or in combination). Dichloroacetate (DCA) has been used in lactic acidosis secondary to mitochondrial cytopathies[80] but no improvement was found either in the symptom severity (as measured in the rating scale) or isometric quadriceps exercise performance in CFS patients as compared to matched controls in a double-blind, placebo-controlled trial of this agent.

Though we have had no experience in the use of immune modifiers, several agents of this class has been tried by other workers[81] but there is no evidence at present that any of these agents (e.g. human immunoglobulin, ampligen) is effective in ameliorating fatigue symptoms. Other treatments tried unsuccessfully in CFS include beta blockers (e.g. atenolol), calcium channel blockers (e.g. nimodipine), opiate antagonists (naltrexone), antivirals (acyclovir), melatonin and magnesium. Oestrogen therapy has recently been claimed to improve symptoms in perimenopausal women with syndrome X,[82] and also with CFS.[83]

PATHWAYS FOR FUTURE RESEARCH

Altered synaptic sensitivities to acetylcholine and serotonin with secondary changes at other receptors, such as glucocorticoid, may explain many symptoms in CFS. At the cellular level, however, neurochemicals act by second messengers and ion channels. In all cases, once neurotransmitters are released into the synaptic cleft, they bind to specific receptors on the post-synaptic target cell and result in a membrane potential change due to the activation of selective ion gates or channels which exist in close physical association with these specific receptors. Thus, ion channels and transporters

play an important role in the maintenance of cellular homeostasis and are essential for normal neurotransmitter function.

It has been postulated that CFS may be caused by viral injury to muscle cell ion channels.[84] Indeed, viruses and toxins appear to be the two commonest precipitants of CFS[3]. Fatigue symptoms similar to CFS are common in asymptomatic HIV carriers,[85] and it is well recognised that HIV-1 gp 120 viral coat protein can alter calcium flux through voltage-dependent calcium channels.[86] Picornavirus (an enterovirus) VP1 and HIV TM contain sequences which induce changes in monovalent cation (Na^+ and K^+) channels.[87] The voltage-gated sodium channel is the major target site for DDT and pyrethroids, the veratrum alkaloids and N-alkylamides.[88] It is thus possible that neuroendocrine abnormalities in CFS and chronic organophosphate-exposed individuals are secondary to membrane-associated receptor dysfunction. Further research is necessary to confirm if there is any abnormal transmembrane ionic traffic in CFS,[79,89] and to clarify whether the observed abnormalities in neuroendocrine axis are due to any persistent and selective changes in neurotransmitter mRNAs.

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