Journal of Clinical Virology 37 (2006) 139–150

www.elsevier.com/locate/jcv

Review

Chronic fatigue syndrome

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Received 24 July 2006; accepted 18 August 2006

Abstract

Chronic fatigue syndrome (CFS) is thought to have a worldwide prevalence of 0.4–1% with approximately 240,000 patients in the UK. Diagnosis is based on clinical criteria and critically depends on exclusion of other physical and psychiatric diseases. Studies of pathogenesis have revealed immune system abnormalities and chronic immune activation, dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis, brain abnormalities, evidence of emotional stress (comprising host aspects) and evidence of exogenous insults, for example, various microbial infections (Epstein-Barr virus, enteroviruses, parvovirus B19, *Coxiella burnetii* and *Chlamydia pneumoniae*), vaccinations and exposure to organophosphate chemicals and other toxins (comprising environmental aspects). Emotional stress appears to be very important as it reduces the ability of the immune system to clear infections, it's presence has been shown to determine whether or not an individual develops symptoms upon virus infection, and it leads to activation of the HPA axis. But, emotional stress is distinct from depression, the presence of which precludes a diagnosis of CFS. There is no specific treatment for CFS other than the much underutilised approach of specific treatment of virus infections. Current priorities are to understand the molecular pathogenesis of disease in terms of human and virus gene expression, to develop a diagnostic test based on protein biomarkers, and to develop specific curative treatments.

Keywords: Chronic fatigue syndrome; Virus; Infection; Diagnosis; Pathogenesis; Gene expression

Contents

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doi:10.1016/j.jcv.2006.08.013

1. Introduction

Chronic fatigue syndrome (CFS) is characterised by a severe debilitating fatigue lasting for at least 6 consecutive months. As well as fatigue, sufferers report numerous other muscular, infectious and neuropsychiatric symptoms as well as sleep disturbances. CFS is thought to have a worldwide prevalence of 0.4–1%, with approximately 240,000 patients in the UK and 800,000 patients in the US (Report, 2002; Papanicolaou et al., 2004). CFS primarily affects women, with a female to male ratio of 6:1. Some studies also suggest that it is more prevalent in the Caucasian population, however, this finding could be as a result of greater access to healthcare in this group rather than an actual increased incidence of CFS in this population group.

2. Diagnosis

The diagnosis of CFS is currently based on clinical criteria. Various case definitions for the diagnosis of CFS exist, however the revised definition of the Centers for Disease Control (CDC) (Fukuda et al., 1994) remains the most widely accepted, particularly for research purposes. CFS is defined by, first, clinically evaluated, unexplained persistent, or relapsing chronic fatigue of new or definite onset (not lifelong); not the result of ongoing exertion; not substantially alleviated by rest; resulting in substantial reduction in previous activities. Second, the concurrent presence of four or more of the following symptoms, all of which must have persisted or recurred during 6 or more months of illness and must not have predated the fatigue; self-reported impairment in short term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social or personal activities; sore throat; tender cervical or axillary lymph nodes; muscle pain, multijoint pain without joint swelling or redness; headaches of a new type, pattern or severity; unrefreshing sleep; postexertional malaise lasting >24 h. It is also critical to exclude physical and psychiatric diseases which may cause fatigue. Further characterization of associated symptoms has also been recommended recently (Reeves et al., 2003).

Currently, there is no laboratory test for CFS, however, this is a priority. Putative protein biomarkers of CFS have been identified using surface-enhanced laser-desorption and ionisation time-of-flight (SELDI-TOF) mass spectrometry (Kerr et al., in press), and if proven to be sensitive and specific indicators of CFS, their discovery may lead to development of a diagnostic test for CFS, which would revolutionise our approach to this disease.

3. Pathogenesis

Although the pathogenesis of CFS is incompletely understood, it is likely to be multifactorial. These factors are best considered in terms of the arbitrary division into host and environmental factors. However, in practice within an individual, these two are clearly interlinked with the presence of particular factors in a particular patient affecting both the likelihood of development of CFS, and also, probably, its phenotype. However, there is no evidence to support this last statement, apart from experience with other diseases, in which, for example, particular gene mutations have been associated with the presence or absence of certain phenotypic features within the umbrella of a particular disease itself.

3.1. Host aspects

3.1.1. Immune response

The observation that the onset of CFS is preceded by virus infections and ‘flu-like’ illness has led researchers to investigate the possible role of immune dysfunction in the pathogenesis of CFS. Numerous immunological parameters have been tested and many are abnormal but inconsistently so among the various studies (reviewed in Natelson et al., 2002). We now recognise that the immune system plays a crucial role in the pathogenesis of CFS, however, the precise role played by the immune response remains to be clarified.

A significant increase in the numbers of B cells expressing CD20 and CD21 markers was found in patients with CFS (Klimas et al., 1990). In contrast, Robertson et al. (2005) have demonstrated that no increase in either total B cells or CD5+ B cells were present in patients with CFS compared to healthy controls. An increase in the number of CD8+/HLA-

DR+ and CD8+/CD38+ T cells have been found in patients with CFS, although the trend was not statistically significant (Robertson et al., 2005). An increase in this class of T cells has also been observed by Klimas et al. (1990). An increased state of differentiation of T cells has been observed in patients with CFS (Straus et al., 1993). However, another study comparing lymphocyte markers in monozygotic twins has shown that there are no statistically significant differences between the twins with CFS and the normal twins (Sabath et al., 2002).

NK cell dysfunction in the pathogenesis of CFS has been widely documented (reviewed in Whiteside and Friberg, 1998). Tirelli et al. (1994) have shown that a subset of natural killer cells (NK cells) were increased as were the total number of circulating B lymphocytes. In contrast, Caligiuri et al. (1987) have shown a deficiency in NKH.1+ T3 cell numbers and decreased NK cell function in patients with CFS who had evidence of EBV reactivation. Klimas et al. (1990) have found a deficiency in cellular immunity in patients with CFS compared with normals. This deficiency manifested as a decrease in the cytotoxicity of NK cells, in spite of an increase in total NK cell numbers. A study measuring NK cell activity in a family with CFS has demonstrated that although total NK cell populations were not reduced in the individuals suffering from CFS, there was a decrease in NK cell activity when compared to healthy controls (Levine et al., 1998). A decrease in NK cell activity as well as a decrease in antibody dependent cell-mediated cytotoxicity has also been observed by Aoki et al. (1993). A number of factors could be responsible for a decrease in NK cell activity, namely, a shift in NK cell populations leading to an increase in the presence of less active cells, a decrease in levels of cytokines that modulate NK cell activity or the presence of an inhibitory factor (Levine et al., 1998).

Various studies suggest that CFS exhibits a Th2 profile of CD4 helper T lymphocyte responsiveness. Visser et al. (1998) have shown that IFN-γ production by CD4 cells from patients with CFS is reduced compared to normal controls. Skowera et al. (2004a) have shown a significant increase in the numbers of CD4 and CD8 T cells secreting IL-4 both following polyclonal stimulation and in resting cell populations from CFS patients compared with those from controls. An increase in IL-4 production in CFS patients has also been shown using neural-network classifiers (Hanson et al., 2001). A Th2 type of immune response has also been proposed (Rook and Zumla, 1997) and observed (Skowera et al., 2004b) in patients with Gulf war syndrome (GWS), which has a similar phenotype to CFS. TGF-β1 mRNA expression appears to be reduced in patients with CFS (Tomoda et al., 2005). TGF-β1 is an anti-inflammatory cytokine and a reduction in the transcription of this protein may increase the likelihood of inflammation observed in patients with CFS. This is also consistent with an infectious process.

Neutrophil apoptosis has been found to be increased significantly in CFS patients as compared with normal controls, lending further support to the theory of ongoing infection in CFS (Kennedy et al., 2004).

Decreases in levels of circulating IgG subsets have been found in patients with CFS. Read et al. (1988) have shown a deficiency of IgG1 in two patients with CFS, with no abnormality in other classes of γ-globulins. Natelson et al. (1998) have shown that IgG1 and IgG3 levels are significantly decreased in patients with CFS as compared with healthy sedentary controls. It was also found that CFS patients with concurrent axis-I depression had lower levels of IgG1 and IgG3 compared with patients with CFS alone. Deficiencies in a number of IgG subclasses have been observed by Komaroff et al. (1988) in patients with CFS, namely, IgG1, IgG3 and IgG4. A decrease in IgG3 levels in some patients with CFS has been observed by Linde et al. (1988). These deficiencies represent a deficiency in anti-viral activity in patients with CFS, and are likely to contribute to the pathogenesis of disease.

The variability observed when measuring immunological parameters in an attempt to elucidate the pathogenesis of CFS may arise from a number of different sources including criteria used for case selection, choice of controls, differences in study design and methodology, etc. (Pedersen and Ullum, 1994).

Taken together, these findings suggest that an underlying infection may be present in these individuals and that the immune system is chronically activated in response.

3.1.2. Endocrine

The hypothalamic–pituitary–adrenal (HPA) axis functions to maintain homeostasis during physical and psychological stress. A disruption of the HPA axis has been implicated in the pathogenesis of CFS (Cleare, 2004). Early studies have shown that cortisol levels in patients with CFS are reduced (Poteliakhoff, 1981), where it is suggested that an initial stress results in a prolonged hyperactivation of the HPA axis, subsequently leading to insensitivity. It appears unlikely that the decreased levels of cortisol observed in CFS patients are due to changes to the metabolic pathway resulting in an increase in the metabolism of cortisol (Jerjes et al., 2006). One proposed hypothesis (Wheatland and Chronic, 2005) is the formation of autoantibodies to adrenocorticotropin hormone (ACTH), which is a positive stimulus for the production and secretion of cortisol by the adrenal glands, and may lead to a decrease in the production of cortisol. It has been suggested that a past or persistent infection can lead to the production of autoantibodies to ACTH.

A link between the immune system and the HPA axis has long been established. IL-6 has been shown to activate the HPA axis leading to increased plasma ACTH and corticosterone in studies on mice (Wang and Dunn, 1998). IL-6 and IL-1 have also been shown to synergistically activate the HPA axis and this is potentiated during emotional stress (Zhou et al., 1996). Conversely, studies have demonstrated that emotional stress can lead to a rise in blood IL-6 levels, thereby resulting in activation of the HPA axis (Zhou et al., 1993).

It is likely that HPA axis dysfunction is not the cause of CFS, but that it is secondary to the primary pathogenesis.

However, once invoked, HPA axis dysfunction may act to contribute towards the perpetuation of the illness (Cleare, 2004).

3.1.3. Brain

Both structural and functional abnormalities have been reported in the brains of patients suffering from CFS. Much interest has focused on altered structure and function of cells in the brain as the cause of fatigue in CFS. The presence of altered cognitive function in patients with CFS has led researchers to investigate the possible role of disorders of the brain in the pathophysiology of CFS. Conflicting evidence exists regarding the involvement of brain abnormalities in CFS. Lesions in the white matter of the brain were found significantly more frequently in CFS patients without depression than in CFS patients with depression (Lange et al., 1999), suggesting that CFS should be divided into subgroups depending on the symptoms. Differences in brain perfusion between CFS patients and depressive patients has been observed (MacHale et al., 2000) suggesting a different mechanism in each case. A study comparing regional cerebral blood flow in monozygotic twins (Lewis et al., 2001), however, has found no significant difference in cerebral blood flow between CFS patients and controls. A decrease in absolute cortical blood flow in patients with CFS has been reported (Yoshiuchi et al., 2006). A decline in gray matter volume proportional to a decline in physical activity in CFS has also been reported (de Lange et al., 2005).

Brain positron emission tomography (PET) studies have confirmed the presence of diminished glucose metabolism in the right mediofrontal cortex as well as significant hypometabolism in the brain stem of CFS patients (Tirelli et al., 1998). These authors speculated that certain herpes viruses, for example, EBV and HHV-6 can accumulate in the brain stem triggering hypometabolism of glucose.

A recent study has also demonstrated a decrease in the number and/or affinity of serotonin receptors in the brain of CFS patients without depression (Cleare et al., 2005). This would lead to an increase in the free serotonin levels in the brain, which has previously been reported to result in fatigue (Blomstrand et al., 1988). Significant reduction in the density of serotonin transporters in the anterior cingulate gyrus of patients with CFS has been observed using PET analysis (Yamamoto et al., 2004). A decrease in *N*-acetylaspartate (NAA), a marker for neuronal function has been observed using MR analysis of the hippocampal region of CFS patients compared to controls, however no decrease in hippocampal volume was noted (Brooks et al., 2000). Corticospinal activity has been measured by electromyography in patients with CFS and compared to normal controls; no differences were observed, although simple reaction times were slower in the CFS group (Zaman et al., 2001). A study monitoring brain activity in CFS patients and controls during the performance of simple cognitive tasks has been carried out using functional MRI (de Lange et al., 2004), showing recruitment of additional cerebral regions involved in visual processes in CFS patients.

Researchers have put forward a proposal suggesting that increased blood brain barrier permeability (BBBP) may be involved in the pathogenesis of CFS (Bested et al., 2001). They suggest that viral replication in cerebral endothelial cells can increase BBBP through the action of cytokines. In support of this hypothesis, an increase in choline containing compounds has been found in the basal ganglia of patients with CFS (Chaudhuri et al., 2003) and in the occipital cortex (Puri et al., 2002). An increase in these compounds suggests an increase in cell membrane turnover, which could arise from viral interaction with host cell membranes. The increase in choline is also indicative of an abnormality in fatty acid metabolism, which could also be triggered by a infectious pathogen. Oral supplementation with eicosapentaenoic acid (EPA) has been found to be beneficial in CFS patients, with two studies demonstrating the improvement in fatigue (Puri et al., 2004; Puri, 2004), which is consistent with the anti-viral and immunomodulatory effects of EPA.

3.1.4. Emotional stress

It is known that emotional stress plays an important role in the pathogenesis of CFS. The influence of this is complex and is likely the combined result of an effect on immune responsiveness, the ability of the immune system to control endogenous virus infection, the ability of the immune system to effectively handle and clear new virus infections and an effect on the HPA axis (Glaser and Kiecolt-Glaser, 1998). Emotional stress results in various changes to the immune system. This has been studied extensively in medical students and includes decrease in NK cell activity, decrease in interferon-γ production by lymphocytes, decrease in cells expressing IL-2 receptor and IL-2R mRNA, decrease in proliferative responses of peripheral blood lymphocytes to mitogens, decrease in T cell proliferation to EBV polypeptides (memory response), decrease in T cell killing of EBV transformed autoloous B lymphocytes (memory response) and evidence of reactivation of latent herpes viruses (EBV and HSV-1) (Kiecolt-Glaser et al., 1984, 1986; Glaser et al., 1985, 1986, 1987, 1990, 1992, 1993; Glaser and Kiecolt-Glaser, 1985; Tomei et al., 1990). In addition, stress is known to have a significant modulating effect on the pathogenesis of virus infection. Cohen et al. (1991) reported that in human volunteers inoculated with five respiratory virus strains, there was a dose–response curve between amount of stress and development of clinical symptoms and their severity.

The principal means by which this influence occurs is likely to be via the HPA axis. It is known that emotional stress can upregulate the expression of corticotropin-releasing hormone (CRH) through the hypothalamus, which stimulates production and release of adrenocorticotrophic hormone, which in turn result in release of hydrocortisone which then downregulates immune responses. These hormones have

been shown to enhance lytic infection with EBV in vitro (Glaser and Kiecolt-Glaser, 1998).

Therefore, emotional stress is known to influence immune responsiveness and virus pathogenesis, and has profound importance to our understanding of the pathogenesis of infectious diseases and cancer, and may therefore be a key aspect in the pathogenesis of CFS.

However, it must be emphasized that emotional stress is not the same as depression, which is an exclusion criterion for a diagnosis of CFS.

3.2. Environmental aspects

3.2.1. Infection

The fact that many cases of CFS begin with a flu-like illness alerted clinicians and researchers to the possibility that this illness could be triggered by infection. This has subsequently been shown to be the case using various approaches. First, it has been possible to confirm the presence of infection in patients with CFS patients who present to the clinic many months after the onset of their illnesses (Chia and Chia, 2003). Second, outbreaks of CFS have been documented which have been shown by laboratory investigation to be caused by outbreaks of particular infectious agents, for example, with *C. burnetii* and enteroviruses (Ayres et al., 2002; Chia, 2005). Third, when a cohort of patients suffering from acute infection with a particular infectious agent are followed in time, a subset of these have been shown to develop CFS with an onset contemporaneous with the onset of the particular microbial infection. For example, parvovirus B19 and Epstein-Barr virus (Kerr et al., 2001, 2002; White et al., 2001).

Numerous studies have investigated the role of infections in the pathogenesis of CFS and various viruses and virus groups have been implicated in CFS at some time; these include Epstein-Barr virus (EBV), cytomegalovirus, parvovirus B19, *Brucellae*, *Toxoplasma gondii*, *C. burnetii*, *C. pneumoniae*, human herpes virus-6 (HHV-6), group B coxsackieviruses (CVB), human T cell leukaemia virus II-like virus, spumavirus, hepatitis C virus, human lentiviruses and herpes virus-7. These are summarised in Table 1, and some important aspects and opportunities for management of such cases are discussed below.

It is likely that virus infection plays a role in a majority of cases of CFS. As with other diseases, early beliefs that CFS may be triggered or caused by a single virus have been shown to be unsubstantiated. Instead, it is clear that various different microbial infections can trigger the disease, and it is likely that different viruses affect different individuals differently, dependent on the host genetic make-up and the immune competence of the individual, which is dependent on various factors including immunosuppression, emotional stress, previous infections, etc. It appears that viruses may trigger CFS by either a hit-and-run mechanism (in which the virus is present at the beginning of the illness but cannot be detected later in the illness) or through a persistent infection (in which the virus is present both at the beginning of the illness and and after months or years and is detectable in patients with CFS presenting to the clinic).

3.3. Infections triggering CFS for which an established treatment exists

Currently, we do not understand the precise pathogenesis of CFS and there is therefore no specific treatment available for CFS patients. However, infections are known to trigger and perpetuate the disease in many cases. Therefore, one potentially valuable approach which has not yet been widely adopted in the management of CFS patients is to exhaustively investigate such patients in the hope of identifying evidence for a specific persistent infection. If such evidence is found, then a trial of the relevant anti-microbial drug(s) may then be warranted. There are many infectious agents which are known to trigger and perpetuate CFS, and which have been or may be targetted with anti-microbial therapy. In some of these instances, there has been clear evidence of clinical benefit or cure in infected CFS patients. Some of these infections are discussed in more detail below.

Table 1
Virus infections which have been associated with development of CFS

Infectious agent linked with CFS	Is persistence a feature of this infection	Treatments used for this infection in the context of CFS	References
Enteroviruses	Yes	Interferons α, γ	Yousef et al. (1988), Gow et al. (1991), Clements et al. (1995), Chia (2005), Chia and Chia (2003), Lane et al. (2003)
Epstein-Barr virus (EBV)	Yes	Valacyclovir	Jones (1988), Straus et al. (1985), White et al. (2001), Lerner et al. (2002)
Cytomegalovirus (CMV)	Yes	Cidofovir, IVIG	Chia and Chia (2003)
Human herpes virus-6 (HHV-6)	Yes	Cidofovir	Ablashi et al. (2000), Chia and Chia (2003), Nicolson et al. (2003)
Parvovirus B19	Yes	IVIG	Jacobson et al. (1997), Kerr et al. (2001, 2002, 2003)
Hepatitis C	Yes	Interferon/ribavirin	Chia and Chia (2003)
Chlamydia pneumoniae	Yes	Tetracycline, charithromycin	Chia and Chia (1999, 2003)
Coxiella burnetii	Yes	Tetracyclines	Arashima et al. (2004)

3.3.1. Enteroviruses

Enteroviruses are well known causes of acute respiratory and gastrointestinal infections, with tropism for the central nervous system, muscles and heart. Enteroviruses have been reported to trigger approximately 20% of cases of CFS (Yousef et al., 1988; Gow et al., 1991). Antibodies to coxsackie B virus are frequently detected in CFS patients, and enterovirus protein and RNA occur in the muscle and blood of CFS patients (Yousef et al., 1988; Gow et al., 1991; Clements et al., 1995), and their presence has been associated with altered metabolism in the muscle upon exercise in the context of CFS (Lane et al., 2003). Viral persistence through the formation of stable double stranded RNA may explain the apparent discrepancy between an absence of live virion in chronically infected patients and animals along with the presence of enteroviral RNA in the blood or other tissues (Chia, 2005). In addition, interferon-α and interferon-γ act synergistically against enterovirus in vitro, and preliminary studies suggest that this combination may be an effective treatment for patients with chronic enteroviral infection (Chia, 2005).

3.3.2. Parvovirus B19

Human parvovirus B19 is the cause of aplastic crisis in patients with shortened red blood cell survival, erythema infectiosum, arthritis, fetal death and persistent infection in immunocompromised individuals (Kerr and Modrow, 2006). B19 virus infection has been shown to lead to development of CFS (Jacobson et al., 1997; Kerr et al., 1996, 2002). B19-associated CFS developed in 4–13% symptomatically infected persons (Kerr et al., 1996, 2002). In these patients, elevated circulating levels of tumour necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) were reported and are consistent with the chronic immune activation characteristic of CFS patients (Kerr et al., 2001). Most of these patients exhibited circulating B19 DNA at the time of presentation (Kerr et al., 2002) and three were cured by administration of the only specific treatment for B19 infection, namely, intravenous immunoglobulin (IVIG), which also coincided with complete normalisation of cytokine dysregulation (Kerr et al., 2003).

3.3.3. Epstein-Barr virus

EBV is a ubiquitous human virus that is transmitted in saliva. EBV infection in normal individuals causes infectious mononucleosis and a percentage of these go on to develop CFS (Jones, 1988; Straus et al., 1985). Early reports that differences in EBV-specific antibody responses occur in those EBV-infected individuals that develop CFS as compared with those that do not, have been shown to be unsubstantiated (Buchwald et al., 1987). A recent study reports that in 10 CFS patients with persistent EBV infection, use of valacyclovir for 6 months led to a significant clinical benefit (Lerner et al., 2002).

3.3.4. C. pneumoniae

C. pneumoniae is a human pathogen which is transmitted by aerosol droplets and causes community-acquired pneumoniae and various other clinical manifestations. *C. pneumoniae* has been shown to cause CFS (Nicolson et al., 2003; Chia and Chia, 1999, 2003) and patients with CFS with a high prevalence of *C. pneumoniae* persistent infection were shown to respond clinically to treatment with azithromycin (Chia and Chia, 1999).

3.3.5. C. burnetii

C. burnetii is a zoonotic infection which may result in a wide variety of clinical manifestations, including influenza-like illness, pneumonitis, hepatitis, endocarditis and CFS. It is amenable to treatment with a variety of agents. Arashima et al. (2004) observed an improvement in fatigue in patients sero-positive for *C. burnettii* infection following minocycline treatment, although this benefit does not appear to be universal (Iwakami et al., 2005).

3.3.5.1. Toxin exposure. The role of environmental toxin exposure in the development of CFS has been identified and evidence exists for the role of toxins in the development of symptoms of fatigue. Studies have been conducted to monitor the levels of toxins in the blood of patients with CFS with a view to determine whether they have any influence of the pathogenesis of disease. Dunstan et al. (1995) have shown that the levels of organophosphates in the blood of CFS patients were higher than in control subjects and comparable to that of CFS patients with known chemical exposure. It has been shown that ciguatera fish toxin poisoning can lead to CFS and that immunological and HPA axis abnormalities are observed in these patients at higher frequency than patients suffering from CFS following EBV infection (Racciatti et al., 2001). Although acute symptoms of ciguatera poisoning last approximately 1 week, the neurological symptoms may be present for months or even years. The neuropsychological performance of farmers exposed to organophosphates was found to be significantly lower than people not exposed to this toxin (Tahmaz et al., 2003). Stephens et al. (1996) have also demonstrated that exposure to OPs can cause nervous system abnormalities.

Many symptomatic parallels can be drawn between Gulf war syndrome and CFS (Fiedler et al., 1996). GWS is thought to arise from exposure to numerous chemicals. The development of GWS in some, but not all Gulf war veterans, highlights the possibility that genetic predisposing factors are crucial for the development of GWS. Butyrylcholinesterase (BChE) and paraoxonase/arylesterase (PON1) are involved in the binding/sequestration and hydrolysis, respectively, of organophosphates (OPs). Prolonged exposure to OPs is known to inactivate BChE and therefore PON1 remains the only mechanism for detoxification of these poisons. Haley et al. (1999) have demonstrated that a particular mutation in the PON1 gene is highly correlated with development of GWS in Gulf war veterans, and it is possible that patients suffering from CFS also carry this mutation. Mackness et al. (1997) have demonstrated that PON1 mutations do lead to a diminished rate of hydrolysis of paraoxon. The role

of pesticides in the development of neuropsychiatric conditions has been widely documented (reviewed in Kamel and Hoppin, 2004) and it has been shown that exposure may lead to CFS/GWS.

A link between exposure to mould and neuropsychiatric symptoms has been established (Crago et al., 2003).

3.3.5.2. Vaccination. Immunisation of humans with vaccines of many types commonly results in a flu-like illness in which fatigue is routinely present. In addition, immunisation with various vaccines have been reported to trigger CFS. These vaccines include MMR, pneumovax, influenza, hepatitis B, tetanus, typhoid and poliovirus (Lloyd et al., 1988; Symmons et al., 1993; Gross et al., 1995; Grotto et al., 1998; Hyde, 1999; Report, 1993; Vedhara et al., 1997; Chia and Chia, 2003).

The relationship between vaccination and development of fatiguing illness is much better established in the case of GWS, probably because in GWS multiple vaccines were used as part of intensive immunisation schedules. Both Unwin et al. (1999) and Hotopf et al. (2000) have demonstrated a correlation between multiple immunizations during deployment of service personnel to the Gulf and the presence of subsequent ill-health. It has been found that Gulf war veterans who received anthrax vaccination were more likely to develop symptoms similar to CFS when compared to veterans who did not receive anthrax vaccination (Schumm et al., 2002). Pertussis, which is used as an adjuvant in anthrax vaccines in the UK is thought to cause a systemic shift in the immune response towards a Th2 profile (Rook and Zumla, 1997), characteristic of CFS and GWS (Skowera et al., 2004a,b). Pyridostimine is used as an anti-nerve gas agent in Gulf war personnel. It has been demonstrated that the combination of pyridostimine and vaccinations can lead to activation of stress-induced kinases in the brains of mice (Wang et al., 2005). Stress at the time of deployment is also certain to be a contributing factor.

4. Treatment

As we do not understand the pathogenesis of CFS, it is impossible to make specific therapeutic interventions. The one exception to this is in the area of infection. For example, if a particular infection can be identified, then the specific therapy can be used, and this is often beneficial.

4.1. Specific therapies

The fact that CFS is frequently triggered and perpetuated by ongoing microbial infection has led to the proposed approach of exhaustive investigation to find an infectious cause of a patient's symptoms, which may then indicate a specific anti-microbial drug regimen that can be used to eradicate that infection with resultant clinical benefit (Chia and Chia, 2003). There are sufficient infections whose association with CFS is prominent to make this approach a useful one in terms of potential benefit to a large number of CFS patients. For example, Epstein-Barr virus, enteroviruses, parvovirus B19, *C. pneumoniae* and *C. burnetii* (see above). This approach is standard in the management of patients with pyrexia of unknown origin (PUO), often with good results. So, why is it such a barrier for us to apply these simple and universally accepted practices to a disease in which infection frequently plays a major role? Along similar lines, immune-stimulant therapy through weekly injections of staphylococcus toxoid led to marked improvements in the symptoms of patients with CFS suggesting that immune activation was key in the clearance of pathogens (Zachrisson et al., 2002).

Hydrocortisone has been used to correct abnormalities in the HPA axis (Cleare, 2003); this has been shown to lead to a significant improvement in symptoms of disease in CFS patients and a reduction of dehydroepiandrostenedione (DHEA) to normal levels, but may also be complicated by adrenal suppression (McKenzie et al., 1998).

4.2. Non-specific therapies

The use of anti-depressants, NSAIDs, anxiolytic drugs, stimulants, anti-allergy drugs and anti-hypotensive drugs have all been reported, but are not universally beneficial (Afari and Buchwald, 2003). Recently, the use of methylphenidate, an amphetamine-derived stimulatory drug, has been shown to significantly improve fatigue and concentration disturbances in people suffering from CFS (Blockmans et al., 2006). Randomised controlled trials have been carried out to determine the effectiveness of intravenous Ig therapy in the treatment of CFS with conflicting results. Two such studies have reported no beneficial effect of IgG therapy on the symptoms of CFS (Vollmer-Conna et al., 1997; Peterson et al., 1990), however one study has demonstrated a beneficial effect of Ig therapy (Lloyd et al., 1990). IVIG therapy is recognized to benefit individual CFS patients although it is difficult to predict which patients may benefit.

The failure of conventional therapies to provide adequate relief from the symptoms of CFS has led sufferers to experiment with various alternative therapies with markedly differing outcomes (Tharakan and Manyam, 2006; Gregg, 1997; Sekiya et al., 2005; Mears, 2005; Sackner et al., 2004; Weatherley-Jones et al., 2004; Ernst, 2004).

The TNF-α inhibitors may provide benefit in CFS. This group of drugs has been shown to lead to dramatic improvement in patients with rheumatoid arthritis, Crohn's disease, psoriasis and other diseases including asthma. One TNF-α inhibitor (etanercept) has been used with significant benefit in the treatment of 6 CFS patients in a pilot study (Lamprecht et al., 2001). Unfortunately, this trial was not published as a paper, but only as a meeting abstract. This requires urgent confirmation in a larger subset of patients.

4.2.1. Psychological therapies

Graded exercise therapy (GET) and cognitive behavioural therapy (CBT) remain the most common methods of treatment for CFS available on the NHS. The rationale for GET is that increasing amount of exercise will 'blow out the cobwebs' and return the patient to a normal or near-normal level of activity. The rationale behind CBT is that patients are encouraged to gain insights into the effects that particular activities have on their physical functioning, and thereby to gain an increased ability to tailor their activities to their capabilities. Numerous studies have been conducted to determine the effect of graded exercise therapy on patients with CFS despite the fact that it is known to have a detrimental effect on many patients. While some studies report benefit of CBT, this is admitted by it's proponents to be a minor benefit and not a cure. In addition, a significant proportion of patients show no improvement following CBT (Akagi et al., 2001; Huibers et al., 2004). Neither GET nor CBT are specific treatments for CFS, as we do not yet understand the pathogenesis of CFS.

Preventing serotonin uptake has been found to be beneficial in CFS patients with secondary depression. A pilot study investigating the possible beneficial effects of the use of the serotonin receptor antagonists, tropisetron and ondansetron on fatigue in patients with CFS showed improvement in fatigue but not any other symptoms (Spath et al., 2000). The use of a serotonin receptor antagonist, granisetron, has shown promising results with regard to fatigue levels, albeit in a pilot study with no placebo (The et al., 2003). The use of the serotonin receptor antagonist, nefazodone, has shown improvements in symptoms of pain and insomnia in all three patients and two of the three patients also showed improvements in NK cell function (Goodnick and Jorge, 1999).

4.3. Supplements to support normal physiology

The use of vitamin and mineral supplementation is very common in those suffering from CFS and is in our view advisable if high quality preparations are used. In addition, use of anti-oxidants in these preparations is of clear benefit due to their role in reducing inflammation and the toxic effects of superoxide radicals and excessive oxidation, which is recognised as a problem in CFS (Kennedy et al., 2005). For example, a 2-month trial with L-carnitine has shown improvements in fatigue in patients with CFS (Plioplys and Plioplys, 1997). The use of L-glutamine is also advisable to aid in repair of the gastrointestinal tract (GIT) and to reduce the catabolic effects on muscles of a debilitating illness. It is known that a deficiency in essential fatty acids may lead to impairment of the immune response due to a decrease in production of cytokines. In this regard, oral supplementation with eicosapentaenoic acid has been found to be beneficial in CFS patients, with two studies demonstrating the improvement in fatigue (Puri et al., 2004; Puri, 2004), which is consistent with the anti-viral and immunomodulatory effects of EPA.

5. Current priorities in CFS

There are currently three priorities in the area of CFS research; to understand the pathogenesis, to develop a diagnostic test and to obtain effective treatments.

5.1. Understanding the pathogenesis

Information generated by sequencing of the human genome along with advances in manufacture of automated chips and data analysis has provided the potential to correlate the genome of an organism with its biological functions. Analysis of gene expression in peripheral blood white blood cells has become a standard methodological approach to study of the pathogenesis of many human diseases and these studies are ongoing in CFS. Considering those studies of gene expression in CFS in which results have been confirmed using PCR (Powell et al., 2003; Kaushik et al., 2005; Grans et al., 2005, 2006; Kerr et al., unpublished), the genes identified in CFS suggest a complex picture but most prominent within which is 'immunity and defense'. This supports previous findings on the role of the immune system in the maintenance of this disease.

But the ultimate goal in all of these studies has not yet been achieved; namely to identify with complete certainty those genes whose overexpression or underexpression occurs in patients with CFS, but not in either normal persons or in patients with other diseases. In addition, such research must be comprehensive enough to identify particular metabolic pathways that are involved in CFS. Therefore, we must use methods that look at all known genes and then be able to group the genes together so that we have knowledge of the pathways involved. This work is ongoing in our Department (Kerr et al., in press) and in several other laboratories. Once we have a clear picture of the metabolic pathways which are abnormally activated or deactivated in CFS, we can then consider options for molecular intervention in order to correct the abnormalities and, hopefully, restore normal function.

5.2. Development of a diagnostic test

Progress is also being made towards identifying biomarkers in the serum of patients with CFS. A biomarker is a protein that occurs at different levels in the serum of patients when compared with normal people and patients suffering from other diseases. This work is being done using SELDI-TOF mass spectrometry (www.ciphergen.com). In this technique, minute amounts of serum are spotted onto the surface of aluminium chips which are then subjected to an ionisation current. This method combines chromatographic separation, achievable due to the presence of biochemically active chip surfaces, with mass spectrometry. Based on the time-of-flight, the mass/charge (m/z) ratio for each molecule is determined. The method is able to determine the mass and relative amount of each individual molecule in complex protein mixtures. Analysis of mass spectra from cases as compared with con-

trols, identifies peaks (or proteins) the presence or absence of which can reliably distinguish between the two groups. It is these proteins (or combinations of them) which can then be used as biomarkers in a diagnostic test, assuming they are shown to be specific to patients with CFS.

The development of such a test, in either ELISA or dipstick format, would revolutionise the diagnostic process in patients with CFS through simplifying it and, hopefully, reducing the need for exhaustive exclusion of a long list of other disease which may also cause fatigue.

5.3. Development of effective treatments

Knowledge of how a disease is caused leads directly to design and utilisation of treatments which correct the abnormal processes and, hopefully, lead to improvement or cure of the disease. In the context of genomic research, many treatments have been designed in this way. For example, a range of so-called 'biologic' treatments are now available for immune-mediated diseases.

On the basis of the results of gene expression studies, and what is known of the pathogenesis of CFS, a clinical trial of interferon-β (IFN-β) is planned at St. George's University of London. We envisage that this will be first of several clinical trials that are based on our gene expression findings, using the novel gene approach outlined elsewhere (Kerr et al., in press).

Acknowledgement

We thank the CFS Research Foundation for funding of this work.

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