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Chronic fatigue syndrome – A neuroimmunological model

S.V. Arnett *, L.M. Alleva, R. Korossy-Horwood, I.A. Clark

Research School of Biology, Australian National University, Australia

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ABSTRACT

The aetiological and pathophysiological basis of chronic fatigue syndrome (CFS) remains a controversial field of inquiry in the research community. While CFS and similar disease conditions such as fibromyalgia (FM) and post-infectious encephalopathy have been the focus of intense scrutiny for the past 20 years, results of research were often contradictory and a cohesive pathological model has remained elusive. However, recent developments in understanding the unique immunophysiology of the brain may provide important clues for the development of a truly comprehensive explanation of the pathology of CFS.

We argue that CFS pathogenesis lies in the influence of peripheral inflammatory events on the brain and the unique immunophysiology of the central nervous system. There is also evidence that CFS patients have a relative immunodeficiency that predisposes to poor early control of infection that leads to chronic inflammatory responses to infectious insults. The neurological and endocrine changes have been described in CFS patients support the view that CFS has an inflammatory pathogenesis when considered as a whole. An inflammatory model of disease also provides an explanation for the marked female sex bias associated with CFS.

This review therefore posits the hypothesis that CFS as a disease of long-term inflammatory processes of the brain. We will also provide an investigative framework that could be used to justify the use of anti-TNF biological agents as a reliable and effective treatment approach to CFS, a syndrome that to date remains frustratingly difficult for both patients and health care professionals to manage.

Introduction

Persistent post-infectious fatigue states have been recorded in scientific literature as far back as the 1930s [1]. The term chronic fatigue syndrome (CFS) was introduced into the medical lexicon in 1988, and is now the most common term used to label persistent fatigue syndromes despite ongoing debate regarding its legitimacy and accuracy [2]. Estimates of prevalence of chronic fatigue/myalgic encephalomyelitis vary between 0.2% and 0.4% [3] and up to 80% of patients are women [4]. CFS is often considered as a diagnosis when efforts to identify a causative agent have failed. At present CFS is a clinical diagnosis, commonly made using the Fukuda criteria [5]. The criteria are as follows; unexplained persistent or intermittent chronic fatigue that is of new or definable onset, fatigue not the result of an identified ongoing exertion, is not ameliorated by rest, and results in reduced participation in personal, social or professional activities. In addition to these criteria, at least four of the following symptoms must be reported to have developed with or following the above symptoms; self-reported impairment of short term memory and/or concentration, sore throat, tender cervical and/or axillary lymph nodes, muscle pain, the emergence of a new pattern of headache, multiple joint pain lacking signs of swelling or erythema, unrefreshing sleep, and a post-exertion malaise that lasts more than 24 h [5]. The post-exertional malaise is considered to be the most indicative secondary symptom in the diagnosis of CFS [6,7]. Fatigue, headaches and impaired concentration are the most common symptoms, affecting 90% of patients, followed by sore throat (85%), tender lymph nodes (80%) and musculo-skeletal pain (75%) [8]. Research into the use of biomarkers for the diagnosis and monitoring of CFS has made substantial advances in recent years. While their use has not reached the clinical setting yet, there is now evidence of altered gene expression profiles [9], markers of inflammation and oxidation [10,11] and other changes such as lowered serum co-enzyme Q10 [12] with the potential for use in the evaluation and management of CFS patients. Clinical similarities are apparent between CFS and other disease conditions including myalgic encephalomyelitis, fibromyalgia, post-infectious fatigue, multiple chemical sensitivity, chronic pelvic pain, temporomandibular joint dysfunction and Gulf War Illness [13,14]. The relationships between these conditions, particularly in terms of pathogenesis, pathophysiology and management strategies, are a subject of ongoing investigation. There are concerns that similar conditions are incorrectly being considered as synonymous – while the above syndromes may have a similar clinical presentation, it has been shown that there are important differences between patients identified using different diagnostic criteria [15]. Even within CFS alone there is mounting evidence

* Corresponding author. Tel.: +61 407 428 389; fax: +61 2 61250313.
E-mail address: simon.arnett@anu.edu.au (S.V. Arnett).

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of distinct disease entities that may have significant implications for diagnosis and management [9].

CFS is commonly precipitated by an acute infectious inflammatory event, and an association with Epstein-Barr virus is widely identified even outside the medical community. However, attempts to associate onset of CFS with a single causative agent, either Epstein-Barr virus or another pathogen, have been unproductive [14,16–19]. Obtaining a significant improvement in symptoms in a clinical setting has proven difficult; only 6–15% of patients report complete resolution of symptoms [20,21] and anywhere from 8% to 63% of patients feel that symptoms improve with time [20]. Generalised pharmacological interventions are considered ineffective in managing CFS patients [22]. However, it has been demonstrated that a more targeted approach involving identification and treatment of underlying chronic infections produces substantial benefit in symptoms in some patients [18]. To date, only two management strategies have found their way into widespread clinical practice; cognitive behavioural therapy (CBT) and graduated exercise therapy (GET) [23]. The use, efficacy and potential adverse effects of these interventions will be discussed in later chapters.

Recent years have provided a remarkable expansion in research into the immunophysiology of the brain. Notably, a substantial body of literature now implicates inflammatory mediators such as tumour necrosis factor (TNF) in the pathogenesis of disorders such as Alzheimer's disease [24–30]. The recent review by Clark et al. [31] has compressed this body of literature into a model of the Alzheimer's disease process, explaining the link between the pathophysiology of the disease and the long-term presence of inflammatory mediators within the brain. Upon review of this literature we have noted that the known physiological derangements associated with CFS are also suggestive of the presence of inflammatory mediators. We propose that this long-term inflammation leads to both neurological dysfunction and patient symptoms, due to the intimate functional association between the immune and nervous systems. The following proposal is a summary of this new disease model and extrapolation to what may be a new generation of efficacious treatments for CFS. Suspicion of a possible causal link between peripheral inflammation and the pathophysiology of CFS has been raised by other authors; the recent article by Maes and Twisk [32] also discusses the evidence of an aetiological relationship between the two, and compares it to the competing biopsychosocial models of the disease.

Hypothesis. Evidence supporting a neuroimmunological model of CFS.

Inflammatory precipitants of CFS

The association of EBV infection with development of CFS is widely recognised, even outside the medical and research community. However, while there is an association of the syndrome with preceding EBV infection, not all patients who contract EBV develop CFS, or even the archetypal severe flu-like illness. A large proportion of the population is sero-positive for EBV but cannot identify an acute episode of infectious mononucleosis [33]. Other efforts to link CFS to a particular pathogen have similarly failed [16,17,34]. Instead, a persistent and severe post-infectious fatigue has been associated with an ever-growing list of precipitating organisms, including *Candida albicans, Borrelia burgdorferi*, enterovirus, cytomegalovirus, herpes simplex virus, retroviruses, brucellosis, Q fever, viral meningitis, human herpes virus 6 and Ross River virus [16,17,34]. Furthermore, a large proportion of CFS patients identify an acute illness with flu-like symptoms as the precipitant of their condition [16,35,36]. This has lead to a suspicion by some investigators that a large proportion of CFS cases are the result of an acute inflammatory insult [17]. The natural extrapolation of this view is that the pathophysiology of CFS is not the result of the virulence factors of any one pathogen, but is instead the result of an abnormal response to infection. That is not to discount the importance of identifying and managing the precipitating infection, or treating an underlying chronic infection that may be contributing to disease pathogenesis. Investigators have reported that treating an underlying infection produced benefits in disease burden [18,37,38], and that many CFS patients have an underlying chronic infection [39].

Immunophysiology of CFS

The well-documented association of CFS with infectious precipitants has led many investigators to search for an immunological basis of the condition, comparing cytokine production or cellular immunity between CFS patients and healthy controls [4,40–43]. One result that is consistent between investigators is deficient NK cell activation and effector capacity [8,14,40,41,43], an intriguing result considering the role that various infections play in instigating post-infectious fatigue and development of CFS. Conceivably, patients with CFS have an underlying relative immunodeficiency that prevents effective control of pathogen proliferation, leading to a more severe infection and inflammatory response, which in turn paves the way for the inflammatory pathology of CFS. While this difference alone may not be the only determinant of which patients develop CFS and which do not, it is our suspicion that such an immunological difference may be an important deciding factor in the development of CFS as a consequence of infection.

However, the role of NK cell activity deficiency has been questioned by the results of McDermott et al. [44]. A randomised controlled trial of oral administration of a putative NK cell adjuvant, arabinoxylane, failed to significantly improve disease symptoms in CFS patients over an eight week period. However, we do not think that this result rules out NK cell activation deficiencies in the pathophysiology of CFS for several reasons. It has been demonstrated that peripheral inflammatory events can result in inflammatory cytokine concentrations remaining elevated in the brain for at least 10 months [45]. Augmenting the activity of the immune system by stimulating NK cell function might not produce a benefit in CFS patients unless this treatment approach is sustained for at least this length of time. Furthermore, McDermott et al. did not provide evidence that arabinoxylane could stimulate NK cell function *in vivo* in patients, instead relying on observations that the compound had a stimulant effect *in vitro* [44]. According to our model, an NK cell stimulant would be most effective in facilitating early control of infection in patients, limiting the intensity of resultant inflammatory episodes, and therefore preventing the sustained inflammatory involvement within the brain that we suggest underpins CFS pathophysiology.

Most investigators have limited their investigations of cytokine production to peripheral blood and serum, and the results are often contradictory, perhaps the result of methodological differences or the fine scale of differences being examined [4,40]. But perhaps more importantly in CFS it is the influence of peripheral immune activation on immune function in the brain that is central to the pathology of this condition. As outlined above, an inflammatory trigger in the periphery can lead to a sustained bout of immune activation in the brain [45]. Cytokine assays of the cerebrospinal fluid, rather than serum, are therefore likely to be the more important indicators of pathophysiology in CFS. Natelson et al. have shown that IL-8 and IL-10 were significantly elevated in cerebrospinal fluid collected from CFS patients [42]. Both these cytokines are elevated in the long-term after an acute inflammatory event, since their production is induced by TNF and IL-1β [46,47]. Amyloid beta precursor protein (APP) is also up-regulated in the cere-

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brospinal fluid of CFS patients [48], and it has been thoroughly demonstrated that APP-1 expression is driven by TNF [49–52]. Their presence in the cerebrospinal fluid of CFS patients is therefore a possible indicator of chronic immune activation in the brain.

Other important evidence that argues in favour of a role for inflammatory cytokines in CFS is the observed increased production of reactive oxygen species. This is strongly associated with not only the presence of CFS but also the severity of symptoms [10,43,53,54]. Reactive oxygen species are produced during the inflammatory cascade, and have the capacity to interfere with neurological function by interfering with oxidative phosphorylation, an important factor considering the very high metabolic demands of brain tissue. Animal models of CFS have demonstrated a benefit from the use of antioxidants [58]. While the production of reactive oxygen species is not unique to CFS and may lack specificity, assays for their presence may prove useful as an adjunct to the clinical diagnostic criteria or in the ongoing assessment of CFS patients. It should also be noted that nitric oxide, another highly reactive molecule produced as part of the inflammatory response, has the capacity to act as an inhibitory neurotransmitter [55]. It has been proposed that nitric oxide is an important contributor to the pain symptoms commonly accompanying CFS, perhaps as a result of central sensitisation resulting from a depression of inhibitory innervation of pain pathways [56]. Furthermore, factors that increase nitric oxide production also exacerbate CFS symptoms [57].

The unique immunophysiology of the brain

Immune function in the brain differs substantially from the immunophysiology of the rest of the body, and these differences are a crucial part of the neuroinflammatory model of CFS. The brain is described as being 'immune-privileged', that is, exempt from the same regulatory and surveillance mechanisms present in other parts of the body [59]. The innate immune system largely orchestrates immune responses to infection in the brain, even in the later stages of infection, relying on microglia and anti-microbial compounds such as amyloid beta to prevent microbial proliferation [16,60]. This paucity of acquired immune system involvement leads to an unusual long-term persistence of inflammatory responses in the brain parenchyma [45]. Another important aspect of brain immunophysiology in the aetiology of CFS is the presence of numerous transport proteins for inflammatory cytokines in the blood–brain barrier (BBB) that facilitate trafficking of inflammatory cytokines, including but not limited to IL-1β and TNF, into the brain parenchyma [61–64]. These transporters have been revealed to be the extra-cytoplasmic domains of the same cytokine receptors found elsewhere in the body, but lacking the intracellular signal transduction pathway proteins required to mediate inflammatory responses, and they facilitate transport through the BBB via transcytosis [62]. Furthermore, endothelial cells contributing to the BBB express adhesion molecules such as ICAM-1 and VCAM-1 in response to inflammatory stimuli such as LPS, and therefore actively contribute to inflammation of the parenchyma through recruitment of inflammatory cells [63]. The net result of this immunophysiology is the ability of systemic inflammatory events to trigger a persistent inflammatory response within the brain, even if the causative agent behind the inflammation is not present in the brain itself [65,66]. This portrait of the immunophysiology of the brain, coupled with the neuromodulatory effects of inflammatory mediators such as cytokines, potentially explains the remarkable spectrum of pathological changes associated with CFS.

Neurological changes associated with CFS

The presence of a chronic inflammatory process in the brain in CFS patients may be central to explaining several physiological changes seen in patients with this condition. There are indications that CFS is associated with a degree of grey matter loss compared to healthy controls [67–69]. The recent review by Clark et al. [31] makes note of the substantial evidence that the grey matter loss that accompanies Alzheimer's is the result of chronic inflammatory cytokine production in the brain, as TNF in large amounts suppresses neurogenesis and synaptogenesis. Logically, a similar process could underlie the grey matter loss seen in CFS. However, while the degree of grey matter loss in Alzheimer's disease is proportional to the duration of disease [70], the same is not true of CFS [68]. Also in favour of a role for TNF and inflammatory cytokines in the pathogenesis of CFS are the similarities between behavioural and cognitive changes associated with CFS, namely persistent fatigue and lethargy [71] and cytokine-mediated sickness behaviours associated with severe inflammatory conditions such as malaria and influenza (reviewed in Ref. [72].) Increased cerebrospinal fluid concentrations of inflammatory cytokines including TNF, IL-1β and IL-18 are associated with memory and learning deficits as well as inhibition of long term potentiation, potentially explaining the cognitive impairments that have been reported to accompany CFS [73,74].

A chronic brain inflammation model may also account for another aspect of CFS pathophysiology – the hyperserotoninergic state of CFS patients and effects of serotonin selective re-uptake inhibitors (SSRIs) on these patients. Although investigations are often indirect due to the technical difficulties associated with direct assay of brain serotonin production, some evidence argues that the CFS brain is subject to a persistent hyperserotoninergic state [14,75]. However, it must be noted that this state is defined only in terms of synaptic serotonin concentrations, rather than receptor ligation [76]. Adding to the case for a synaptically hyperserotoninergic brain is the anecdotal evidence of increased side effects of SSRI antidepressants in CFS patients, with symptoms bearing a striking similarity to serotonin shock syndrome [35]. This leads to the obvious questions of why the CFS brain is hyperserotoninergic, and whether this causes the development of CFS or arises from an underlying disease process. An argument can be made that the hyperserotoninergic state is a consequence the relationship between serotonin and neurotransmitters such as nitric oxide produced during inflammation. Neurons produce nitric oxide via the activity of the neuronal form of nitric oxide synthase, as a result of NMDA receptor ligation by glutamate [55]. Importantly, the activity of the inducible form of nitric oxide synthase is increased as part of the inflammatory cascade [77]. High nitric oxide concentrations can themselves activate the NMDA receptor and trigger glutamate release [78], and NMDA activation antagonises the serotonin receptor signal transduction pathway [57]. It is also true that inhibition works the other way; serotonin receptor ligation decreases the activity of the NMDA pathway [79]. In other words, the pathways triggered by NMDA and serotonin are mutually antagonistic. It may be that the hyperserotoninergic state is a result of a long-term compensatory mechanism, an attempt to overcome the chronic inhibition of serotoninergic pathways that results from increased activation of the NMDA pathway and other inhibitory molecules in the brain. Again, the pathophysiology of CFS can be traced back to a chronic inflammatory response in the brain. Further complicating matters is the fact that elevated concentrations of pro-inflammatory cytokines increase the rate of serotonin catabolism in the brain, elevating the concentrations of serotonin metabolites [80]. However, the use of SSRIs in the management of CFS patients has produced contradictory results. While several investigators have shown no benefit in the use of SSRIs [81,82], Thomas et al. have demonstrated that long-term SSRI use produces symptomatic benefit in CFS patients and increases the proportion of patients who ultimately recover from the condition compared to patients not using SSRIs [35]. The conflicting data

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may be a result of the duration of the respective studies: Vercoulen et al. followed patients for 8 weeks, whereas Thomas et al. followed patients for up to three years, a point of comparison the latter notes in their publication. A possible explanation for the efficacy of SSRIs may have been provided by Horikawa et al., with the demonstration that SSRIs (paroxetine and sertraline) reduce TNF and NO production by IFN-γ activated 6–3 microglial cells *in vitro* [83]. As a result, SSRIs may make a modest anti-inflammatory contribution to neurological physiology, which if our model of CFS pathophysiology is correct, could be an important factor in understanding the clinical efficacy of SSRIs documented by Thomas et al. There are other possible explanations for the results of Thomas et al., such as treatment of comorbid psychological disorder improving symptoms in CFS patients. However, it has been demonstrated that management of concurrent mental illness, while an important part of addressing patient well-being, does not produce a substantial benefit in CFS symptoms [81]. It should be noted that that immunomodulatory treatments could be problematic in patients with a current infection, and management of such an infection may need to be considered before beginning SSRI therapy.

Endocrinology of CFS

Another focus of research in CFS pathophysiology is exploration of abnormalities of the HPA axis. Again, consensus is less than absolute, but evidence exists of a mild hypothalamus–pituitary–adrenal (HPA) axis suppression involving depressed adrenocorticotropic hormone (ACTH) production in response to psychosocial stress and increased potency of negative feedback of cortisol on the HPA axis [84,85]. Given the immunosuppressive effects of glucocorticoid hormones, it is easy to envisage how hypofunction of the HPA axis could contribute to the inflammatory pathology of CFS by failing to provide a negative regulator of immune function. However, the causality of this relationship also remains unresolved; does a hypoactive HPA axis predispose to CFS, or does the immune dysfunction of CFS progress to involve abnormal function of the HPA axis? We suspect the latter. The degree of HPA axis dysfunction correlates with the length of illness [85], suggesting that the pathology of CFS causes HPA axis hypofunction. Additionally, attempts to treat CFS symptoms with corticosteroids have not been shown to be efficacious, suggesting that HPA axis dysfunction is a result, rather than a cause, of CFS [86]. Furthermore, inflammatory cytokines such as IL-1β can modulate release of corticotropin-releasing factor, the hypothalamic hormone that drives ACTH release [85], potentially altering long-term homeostasis of the HPA axis [87].

Other aspects of endocrine physiology may be an important part of explaining the development of CFS, namely the pronounced sex bias in CFS and related conditions. Exact figures vary, but at least 75% of CFS patients are female. This bias may be at least in part attributable to a clear difference between the sexes in the immune modulation effected by glucocorticoids. These hormones have a more potent immunosuppressive effect on whole blood preparations derived from men than on cells derived from women [88], an effect exacerbated by the oral contraceptive pill [89]. In other words, there is evidence that leukocytes derived from males are more sensitive to the immunosuppressive effects of corticosteroids than leukocytes derived from females. While the exact mechanism behind this difference has not been elucidated, it may be a clue to explain the sex bias of CFS and related conditions. Specifically, if a functional difference between the immune systems of males and females results in a propensity towards an intense pro-inflammatory response to infection in females, and CFS is underpinned by an inflammatory pathophysiology, this sex difference may account for the reported sex bias of CFS.

The use of graduated exercise therapy and cognitive behavioural therapy in managing CFS

As mentioned previously, two therapeutic interventions have found widespread use in the management of CFS – CBT and GET [23]. CBT is the training of CFS patients to recognise exposures and thought processes in their daily life that worsen symptoms, to develop strategies to avoid or limit the impact of these exposures. However, only 20–40% of patients report any improvement following cognitive behavioural therapy, and while it produces some benefit in symptom scores it has not been shown to improve cure rates [90,91]. In comparison, GET is the use of a graduated increase in physical exercise over time with the aim of improving tolerance to physical exertion as well as improving symptoms. However, there have been recent challenges to the validity of using GET in CFS in light of evidence that GET produced a marginal benefit at best and in some cases exacerbated symptoms [92,93]. Most recently, Nunez et al. demonstrated that GET failed to produce a consistent quality of life benefit, but worsened pain and physical function scores for many patients [94]. In contrast, White et al. reported an improvement in mean fatigue scores between patients receiving GET compared to those receiving standard medical care [95]. Both investigators used the short form 36 questionnaire to assess physical function in patients, and post-intervention evaluations were conducted at 12 months in both studies.

The effect of exercise on immune and neural physiology is complex. There is substantial evidence that effects are dose-dependent – sustained exercise regimes with a gradual increase in exertion induce different responses to a sudden bout of high-intensity exertion. The former has been shown to produce an anti-inflammatory effect, depressing serum TNF and increasing serum IL-1 receptor antagonist, soluble TNF receptor and IL-10 concentrations through the actions of IL-6 [96,97]. This immunomodulatory effect is driven by mechanical stress incurred by skeletal myocytes, which are the cellular source of the elevated IL-6 seen in individuals who exercise regularly. Serum IL-6 production is proportional to exercise duration, intensity and force exerted [98]. While IL-6 has been classically regarded as a pro-inflammatory cytokine, there is evidence that it has a substantial anti-inflammatory effect on the immune system; it stimulates IL-1 receptor antagonist production and IL-10 production without increasing production of pro-inflammatory cytokines such as TNF or IL-1β [96]. Furthermore, both IL-6 knockout mice and mice treated with anti-IL-6 monoclonal antibodies show elevated basal serum TNF concentration [96]. Therefore, IL-6 production by myocytes in response to physical stress can exert an anti-inflammatory effect on the immune system. There is also more direct evidence of a physiologically relevant anti-inflammatory effect – a preceding regular exercise program reduces the TNF response to *Escherichia coli* challenge in mouse models [96]. However, the potential pro-inflammatory effects of exercise must also be considered. Exercise increases circulating numbers of lymphocytes, monocytes, neutrophils and NK cells [99], while abrupt high intensity exercise induces production of pro-inflammatory cytokines [100,101]. In healthy individuals the pro- and anti-inflammatory effects of exercise are roughly balanced and no significant adverse effects develop. However, in individuals with underlying inflammatory states such as traumatic injury, infection, atopy or autoimmune disease, the balance is disturbed and exercise has a pro-inflammatory effect (discussed in detail in Cooper et al. [102]).

These considerations may provide an explanation for the unreliable efficacy and potential adverse effects of GET in managing CFS [92,93]. If CFS pathophysiology ultimately lies in inflammatory responses to infection, then the variable pro- and anti-inflammatory effects of exercise could either improve or exacerbate disease symptoms on an individual basis. Explanation of this variable clin-

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ical efficacy may lie in the sub-groupings of CFS patients described by investigators such as Zhang et al. [9]. It may be that patients with less severe persistent peripheral inflammation receive an anti-inflammatory contribution from exercise, but the same exertions are pro-inflammatory in patients with higher circulating cytokine concentrations leading to exacerbation of symptoms. Whatever the explanation, the use of GET in the management of CFS is in serious doubt, and there stands a need to develop a method of identifying which patients respond poorly to physical exercise and should be advised to avoid GET.

Interventions to ameliorate symptoms of CFS

If, as proposed above, CFS has neuroimmunological origins, then anti-inflammatory treatment options may prove efficacious in relieving the disease symptoms in patients. Therefore, there stands a need to assess the efficacy of centrally-acting anti-inflammatory agents in the management of CFS.

We have particular interest in the use of anti-TNF biologicals (infliximab and etanercept), as Tobinick et al. has demonstrated, as yet only in open trial, that etanercept produces a rapid and dramatic improvement in clinical signs of Alzheimer's disease, another disease where a neuroinflammatory mechanism is increasingly implicated, following administration of these drugs [103]. Etanercept works as a decoy receptor for TNF, neutralising the function of this cytokine *in vivo*, while infliximab is a monoclonal antibody that also binds to and impedes the function of TNF. It is used as part of the management of wide variety of inflammatory disorders, and thus we propose that the precedence set in its use by Tobinick et al. [103] is sufficient justification to expand its use in CFS patients. Furthermore, investigations by Tobinick et al. [104] have shown that brain accessibility by large, polar drugs may be potentially overcome with a period of placing the patient in a position in which the head is depressed below the heart following administration of the drug to the vertebral venous plexus, which is continuous with the intraspinal and radicular veins. The lack of valves in this venous circulation allows for transient regional bidirectional flow, delivering the drug to the choroid plexus where it can cross into the cerebrospinal fluid. Animal models have shown that depressing the head below heart following administration of a drug as described above allows for the introduction of radio-labelled etanercept into the cerebrospinal fluid [104]. This method has been expanded to human patients in small scale trials of the use of etanercept in treating Alzheimer's, and the rapid improvement in symptoms noted has been attributed to this aspect of cerebral venous physiology [103]. We also see value in similar assessment of other anti-inflammatory drugs, assuming they lack significant neurotoxicity and are able to reach an effective concentration within the CSF and brain parenchyma.

However, as mentioned previously, a substantial proportion of CFS patients have a chronic infection that may be contributing to disease symptoms [39]. Anti-TNF biologicals could exacerbate such infections and be detrimental to patients if not used with care. It would therefore be prudent to investigate for, and treat, any possible chronic infection in CFS patients before beginning a regime of anti-TNF biologicals.

Conclusions

The individual and societal burdens of CFS and related disease conditions are substantial. Estimates have not been produced for Australia, but projections suggest that CFS alone may cost the United States economy upwards of nine billion dollars annually in lost productivity [105]. CFS and related conditions are debilitating and intractable conditions that often strike patients at a time of their life when they would otherwise be at their most economically and socially productive. These diseases also extract an enormous personal toll, often leading to depression and poor mental health outcomes. Attempts to date to treat CFS have been met with limited success, and the research and medical communities have struggled to make substantial progress in devising a comprehensive model of the pathogenesis of these conditions. The hypothesis provided in this review, that CFS is a result of the presence of inflammatory mediators in the brain, provides a comprehensive explanation of CFS pathophysiology. This unique perspective ties together a large body of experimental evidence regarding CFS into a cohesive model of pathophysiology, that we hope provides a foundation for the development of efficacious treatments of the syndrome.

Conflict of interest statement

The authors declare that they have no personal or financial interests that have influenced the content of this article.

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