

The interface between chronic fatigue syndrome and depression: A psychological and neurophysiological conundrum

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Abstract

The chronic fatigue syndrome (CFS) remains a contentious and controversial presentation despite decades of systematic research from a variety of medical specialties and associated disciplines. Variously championed as a condition of immunological, neurological, neurophysiological, psychiatric or psychological origin, consensus on a cogent and evidenced-based pathway has yet to be achieved. Irrespective of the ambiguity regarding aetiology, what is incontrovertible is the experience of significant depression which often accompanies this most distressing clinical presentation. The current paper examines the potential underlying mechanisms which may determine and explain this relationship between CFS and depression. In doing so, it offers some insights, which may be of value in the development of evidence-based and scientifically-anchored interventions in individuals experiencing this diagnosis, to improve outcomes in relation to depression specifically and quality of life more generally.

Keywords: CFS; depression; fatigue; myalgia; neurophysiological substrates; syndrome

Running title: CFS and depression: mechanisms

L'interface entre le syndrome de fatigue chronique et la dépression: un enchevêtrement psychobiologique et neurophysiologique

Résumé

Le syndrome de fatigue chronique (SFC) reste discutable et controversé malgré des décennies de recherches systématiques de la part d'un grand nombre de spécialités médicales et de disciplines connexes. Diversement défendue comme une condition d'origine immunologique, neurologique, neurophysiologique, psychiatrique ou psychologique, un consensus basé sur une voie convaincante et fondée sur des preuves n'a pas encore été atteint. Indépendamment de cette ambiguïté concernant l'étiologie, ce qui est incontestable, c'est que l'expérience d'une intense dépression accompagne souvent cette présentation clinique des plus affligeantes. Le présent document examine les mécanismes sous-jacents potentiels qui peuvent déterminer et expliquer cette relation entre le SFC et la dépression. Ce faisant, il présente quelques idées qui peuvent être utiles à trouver des solutions basées sur des preuves et des données scientifiquement probantes chez les personnes atteintes de ce syndrome, afin d'améliorer les résultats en relation avec la dépression spécifiquement, et la qualité de vie de façon plus générale.

Mots-clés: dépression; fatigue; myalgie; SFC; substrats neurophysiologiques; syndrome

Introduction

Fatigue is both a ubiquitous symptom and at the same time extremely difficult to define. In many cases the definition of fatigue attempts to identify the underlying cause, for example muscle dysfunction [11]. Whereas other definitions take a more behavioral perspective, treating fatigue in terms of a global loss of function. From a purely physiological perspective, fatigue is the loss of maximal force-generating capacity that develops during muscular activity [41]. The perception of fatigue is subjective and can be described by non-clinical populations as ‘exhaustion’ in relation to the overarching symptoms of depression [61], whereas others may describe fatigue as ‘feeling more tired than usual’ or ‘generally run down’ [27]. Individuals have attributed their feelings of fatigue to the combined features of physical, psychological and social stress [19]. Fatigue may be better understood as a spectrum disorder rather than as a discrete phenomenon, given the clearly subjective nature of perceptions of fatigue [11]. Despite the subjective nature of fatigue, several attempts have been made to produce scales that measure both perception and severity, with mixed success [1, 47]. Many scales have been developed for patients with clearly defined medical conditions, for example multiple sclerosis [23] and cancer [59, 66]. Beurskens et al. [8] developed a 20-item individual strength questionnaire measuring fatigue in a normal working population, but seemed to identify particular individuals with clinical features which included fatigue as part of their symptomatology; the underlying condition was unidentifiable within the study, and beyond the scope of the questionnaire.

Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS) is a condition generally accepted by most clinicians to incorporate the range of symptoms that is also referred to as myalgic encephalomyelitis (ME) or chronic fatigue and immune dysfunction syndrome [51]. In recent years CFS has received much attention in the media and from the medical profession. However, the exploration of CFS has hit many obstacles which include etiology, linguistics and methodological difficulties [11]. For many years, there has been a plea for more precise operational definition and better methodological studies, which include epidemiology and symptomology of fatigue [11].

CFS is a profoundly severe and enduring fatigue that lasts at least 6 months, in which there is no improvement in symptoms following rest, and which may also be exacerbated by physical and mental exertion [12, 24, 45]. Although fatigue is the cardinal symptom of CFS,

it is characterized by several co-morbidities which may include cognitive dysfunction, trouble falling asleep and maintaining sleep, myalgia, headaches, digestive tract dysfunction, sore throat, and painful lymph nodes [12, 36]. Like general fatigue, CFS lacks a known cause and a specific diagnostic test. As such, CFS is generally referred to as a heterogeneous disorder, which may be caused by a multitude of factors. Fatigue severity is associated with a poor prognosis for CFS, because of its correlation with acute somatic symptoms and functional limitations [34].

As a direct consequence of CFS, individuals will often report substantial loss in physical and social function, as well as economic disability [12]. Those with CFS may report financial difficulties due to lost or reduced employment opportunities, and alongside an increased risk of unemployment is the associated risk of depression [54].

CFS has about 0.3% prevalence in the general population, which amounts to about 972,000 individuals in the USA, and roughly 195,000 individuals in the UK. However, the prevalence is thought to be much higher because of the multifaceted way in which the condition is diagnosed; as such the rate could be as high as 3.3% [57] and therefore the actual figure could be as high as 10,692,000 individuals in the USA, and 2,145,000 individuals in the UK. As a consequence of diagnostic challenges and because patients often present with a multitude of symptoms, treatment approaches have been broad and included immunologic, pharmacologic, behavioral treatment and complementary and alternative medicines [57]. To date no medication has been specifically developed for the treatment of CFS, and many generalized treatments are off label (without specific review or approval). These generally treat symptoms such as pain, autonomic dysfunction, sleep dysfunction and associated psychiatric conditions such as depression. CFS patients may even receive immune modulators, antiviral medication and antibiotics [22]. In reality the clinical management of patients varies widely and many patients receive a multifaceted approach to treatment [57].

One of the major impediments to fully understanding CFS is the absence of confirmatory physical signs or biological tests. This lack of diagnostic consensus has led to an enduring debate as to the true etiological nature of the condition [12]. The debate historically supports two principal pillars: psychiatry and psychology. Individuals with CFS may report mood disorders, affective and behavioral dysfunction (neuropsychiatric issues), and/or cognitive abnormalities (neuropsychological issues). Because there are considerable psychiatric and psychological commonalities within CFS patients, there is an assertion that CFS is a form of atypical depressive illness [12].

Depression

Depression is a multifactorial condition brought about by biological, psychological, and social factors [49]. According to the diathesis stress model, depression is a consequence of stressful life events imposed on a pre-existing vulnerable condition [62]. The handbook of mental disorders, the DSM-5 [5] defines depression under the section entitled Depressive Disorders. Depressive disorders include disruptive mood regulation disorder, major depressive disorder, persistent depressive disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, and unspecified depressive disorder. Major depressive disorder represents the classic condition; it is characterized by discrete episodes of at least 2 weeks' duration, in which significant changes in affect, cognition and neurovegetative function occur and time between remissions decreases noticeably [5]. The cardinal feature of all depressive disorders is the presence of sad, empty, or irritable mood, and significant loss of individuals' competency to function. Defining features of all depressive disorders are their duration, timing and etiology [5].

When individuals are diagnosed with a depressive mood disorder the course of treatment will invariably involve pharmacological treatment. Selective serotonin reuptake inhibitors (SSRI) tend to be the most widely prescribed type of antidepressants.

SSRIs tend to increase the extracellular level of the neurotransmitter serotonin by limiting its reabsorption into the presynaptic neuron. Serotonin-noradrenaline reuptake inhibitors (SNRI), they are thought to work in the much same way as SSRI, but with the action of also limiting the reuptake of noradrenaline. Tricyclic antidepressants (TCA) work primarily by increasing levels of norepinephrine and serotonin. The clear majority of patients treated with antidepressants will see an improvement; however antidepressants tend to come with some serious side-effects. SSRIs and SNRIs, are thought to cause feelings of agitation and anxiety, can make the individual feel sick with lethargy and digestive problems (stomach aches often accompanied by diarrhea or constipation), and contribute to weight gain.

Neuropsychiatric Features of Chronic Fatigue Syndrome with Depression

CFS is associated with numerous neuropsychiatric co-morbidities, which are primarily related to mood, affect and behavior [12]. It has been estimated that at least 60% and possibly 70% of those with CFS will also have significant psychiatric conditions, specifically depressive disorders [33]. Fuller-Thomson and Nimigon [25] conducted a large-scale study exploring the prevalence of depression among a population of individuals with CFS, and

found that more than a third (36%) of individuals reported significant depressive symptoms, low levels of mastery, and low self-esteem. In another study, Buchwald et al. [9] found that 22% of their patients with CFS had a current diagnosis for major depressive disorder and 73% had a lifetime prevalence for major depressive disorders. Both studies [9, 25] also found additional neuropsychiatric symptomatology for anxiety disorders and somatization disorder at significant levels, in CFS patients.

Chronic Fatigue Syndrome and Depressive Illness

Depression is a major cause of morbidity and mortality, which is correlated with impaired health-related quality of life and social functioning [17, 26, 58] with associated physical disabilities [21, 39]. Many psychiatric conditions, particularly depressive illnesses, are often related to an increased prevalence of chronic diseases, in which the depressive state can precipitate or exacerbate these co-morbidities [60]. Even though depressive illness can be successfully treated with antidepressants and psychotherapy, most individuals do not seek appropriate medical help, or if they do seek help they often receive inappropriate care, particularly if they are male, black, less well educated, younger than 30 or older than 55 [67].

CFS and depressive illness share specific symptoms [63] such as fatigue, sleep disturbances, poor concentration and memory difficulties. [40]. For a high number of patients with depressive illness there is also a pain dimension [7] which appears to suggest a common neurobiology pathway between CFS and depression. For these reasons, it has been argued that both conditions may be part of a stress-related spectrum disorder [7].

However, the precise pathway that links CFS and depressive illness is still part of an intense and very controversial debate [12]. The debate has three points of focus. The first is that depressive illness is found in most patients with CFS; therefore, CFS has been described as atypical depression. The second area of focus explores whether depressive illness within CFS simply exists because of the physical toll that CFS has on the patient. The last focus is shared etiology, since both CFS and depressive illness share the same or similar factors which cause the underlying condition [6]. The debate exists because of both conditions share lack of physical signs, subjective nature of symptoms and lack of a universally accepted etiology. This has led some to argue a psychiatric etiology, but in doing so has further polarized the debate [55]. Symptoms of CFS principally rely on subjective reports from the patient, and it is the subjective nature of CFS symptoms that has primarily fueled the controversy: is the underlying etiology of CFS organic or psychogenic [37]? The reality is

that CFS is a chronic disabling condition, which in most cases includes depression among the long list of symptoms [12].

Chronic Fatigue Syndrome and Major Depressive Disorder

Major depressive disorder (MDD) is a neuropsychiatric disorder that is characterized by pathologically low mood, reduced hedonic responses, poor motivation, fatigue and impairment in concentration sleep and appetite [48]. MDD and CFS share significant symptomatology, invariably comorbid, and they also share risk and precipitating factors [3]. Even though MDD is significantly correlated with CFS, in about 50-70% of case there are no co-existing psychiatric symptoms of MDD [64, 65]. This is an important point: even though MDD can coexist with CFS, it is not always present and so cannot be used a diagnostic marker for CFS [20]. Additionally, patients with CFS may meet the diagnostic criteria for MDD or score in the depressed range on self-report inventories, but the type of depressive symptoms reported may be qualitatively different from those reported by individuals with clinical depression [37]. CFS may be difficult to differentiate from clinical depression, but studies have shown that symptoms are described differently between patients with CFS and those with MDD [12]. Patients with CFS primarily complain of physical somatic symptoms of fatigue, while patients with MDD generally identify with symptoms of disturbed mood and self-reproach [37]. Johnson et al. [37] found that patients with CFS reported a significantly higher percentage of somatic complaints than patients with MDD alone. It was felt that somatic symptoms (physical appearance, fatigue, inability to work, health concerns) were primarily related to physical signs of CFS. Patients with CFS will also complain of post-exercise myalgia, and resting myalgia. Whereas patients with MDD will often report severely impaired self-esteem, in the CFS patients self-worth is well preserved [50]. Powell et al. [50] suggest that poor self-esteem in depressed patients is a reflection of the severity of the mood disorder. This is also reflected in the observation that depressive individuals were severely more depressed than CFS-depressive patients [50]. It has been shown that the pattern of symptom attribution is different between patients with CFS and MDD. Most CFS patients attribute their illness to physical causes, whereas those with affective disorder tend to attribute to their symptoms to psychological causes [65], which is not at all together surprising given the nature of both conditions.

It has been suggested that symptoms attributed to externalities are thought of as being less disabling than symptoms attributed to personal or internal causes [4]. Externalizing the

attribution of specific symptoms may exert a protective influence against certain cognitive changes of depression, as opposed to an internal style of attribution causing the patient to experience greater psychological stress and low self-esteem [50, 53]. There is also a protective measure in guarding against being labeled with a psychiatric disorder. However, when CFS patients attribute their condition to external causes, this appears to lead to feelings of helplessness, increased fatigue, lack of self-efficacy and diminished responsibility for one's own health [50]. Patients with an external locus of control reported more depressed mood and higher levels of state anxiety, indecisiveness, fatigue, agoraphobia and somatic symptoms [32]. It has been almost 40 years since Abramson et al. [2] formulated their learned helplessness model of depression. This model postulated that individuals vulnerable to clinical depression should cultivate an internal, stable, and global style of attribution. Powell et al. [50] found that patients with CFS attributed their underlying condition to external states, which were reported to be potent, uncontrollable, aversive and frightening. According to Powell et al. [50], this predicts a high rate of depression.

Studies consistently show that CFS and depressive patients share specific symptom similarities, which may include fatigue, pain, sleep disturbances and poor concentration. However, studies also consistently show that although the two conditions may share commonalities, they are distinctly different conditions [6, 12, 35]. An example of this is that CFS and depressive patients differ in regard to their response to physical exertion. Silver et al. [56] conducted a study in which they were interested in beliefs in relation to avoidance of physical activity. Previously chronic pain studies had examined the fear or avoidance of physical activity and found that fear and avoidance were more disabling, to the individual, than the pain itself [18]. Silver et al. [56] also found that CFS and depressive patients report a response to physical exertion differently; CFS patients experienced an increase in fatigue symptoms post-exertion, while on the contrary depressive patients experienced a positive increase in their mood.

Chronic Fatigue Syndrome and Depression: their Shared Biology

It is clear that there is a significantly shared co-morbidity with depression and CFS [43]. It is also clear that depressive symptoms frequently coexist during the course of CFS [37]. Likewise it is evident that fatigue and somatic symptoms, which may include pain, muscle tension, and flu-like malaise will often be reported in courses of depression [43]. However, despite the shared clinical features there are significant dissimilarities between the two

conditions, so much so that they are considered separate illnesses. Maes [43] suggests that depression and CFS are not co-morbid disorders but should be regarded as co-associated disorders that are clinical manifestations of shared pathways. Numerous studies have shown that depression and CFS share aberrations in inflammatory, oxidative, and nitrosative stress (IO&NS) [12, 43]. The IO&NS pathway is a complex succession of biochemical reactions, which may result in damaging free radicals and nitric oxide effects at the cellular level [12, 40]. These pathways are stimulated by several trigger factors, which may include psychological stress, strenuous exercise and viral infection [42]. Maes, Mihaylova, and Leunis [44] found that IO&NS damaged DNA, proteins and fatty acids, and was also associated with complaints of fatigue, muscle pain, and flu-like malaise. Taken together it would seem that CFS and depression may share a common pathway in regards to IO&NS, which may account for the similar clinical features.

Evidence has also been presented which implicates another biological system in the onset and maintenance of both CFS and depression: that of the hypothalamic-pituitary-adrenal (HPA) axis. Much biological research has focused on the HPA axis, with evidence of reduced cortisol output in CFS patients, which is been detectable by sequential salivary samples [14]. Cortisol replacement has been found to ameliorate symptoms of fatigue and other signs of CFS [16, 46]. However, in most studies, patients with symptoms of CFS have been ill for many years; as such it is not clear whether HPA axis disturbances were present before the onset or occurred early on in the time course of CFS, nor is it clear to what extent observed HPA axis disturbances are secondary to inactivity, sleep disturbances or deconditioning or stress [15]. Roberts et al. [52] argue that it is possible that there is a vicious cycle present, one in which low levels of cortisol may exacerbate fatigue and other symptoms, which in turn leads to worsening of some of the factors that had initially contributed to lowered levels of cortisol. Whereas CFS is associated with low levels of cortisol, the opposite is true of depression. MMD is classically associated with increased HPA axis activity and increased levels of cortisol [30]. Studies have reported an association between cortisol secretion and cognitive function in medication-free depressed patients. Depressed patients with increased cortisol levels are impaired in verbal memory, visual spatial memory, working memory, and selective attention. Deficits were also reported in relation to hippocampus-associated neuropsychological domains such as verbal memory, visual spatial memory and executive functioning [29].

What is clear from the studies considered above is that CFS and depression share common symptoms, outlined by commonalities in shared aberrations in inflammatory,

oxidative, and nitrosative stress (IO&NS) but there is evidence to support the notion that CFS and depression are distinctly different conditions. Evidence shows distinct differences in HPA axis functioning and the release of cortisol, and the administration of cortisol that ameliorates symptoms of fatigue and other signs of CFS. In contrast in a depressed population cortisol levels are increased, which appears to cause problems with memory and executive functioning.

Neuropsychiatric Co-morbidities of Chronic Fatigue Syndrome

CFS is associated with several clinical features including fatigue, which imposes substantial loss in physical and social function, alongside economic disability [12]. As such it has been suggested that depression in CFS is a natural response to the debilitating symptoms experienced by patients [12]. CFS patients have reported being more functionally impaired than individuals with multiple sclerosis, coronary heart disease, type-2-diabetes and acute myocardial infarction [9, 13, 38]. Hickie et al. [28] observed the prevalence of psychiatric disorders in patients with CFS, and found a small percentage had a current diagnosis for major depressive disorder, equal to that normally expected in the general community. They also report that CFS patients were not excessively hypochondriacal, and concluded that psychological disturbances are likely to be a consequence of, rather than an antecedent risk factor to CFS.

Ciccone et al. [13] suggest that psychiatric factors could be linked to differences in functioning based on psychiatric illnesses prevalent in both tertiary and primary care. Johnson et al. [37] found that 45% of CFS patients in tertiary care met the criteria for a psychiatric illness, whereas Buchwald et al. [9] found that the figure was nearer 82%. Within a primary care setting the figures range from 45% [10] to 60% [31]. Ciccone et al. [13] argue that just because studies have failed to find differences in physical functioning between depressive and non-depressive CFS patients [38], this does not rule out the possibility that CFS patients might have a comorbid personality disorder. They argue that personality disorder may count for impaired functioning in a subset of CFS patients. Ciccone et al. [13] report that 35% of individuals with CFS met the criteria for a personality disorder. However, Ciccone et al. [13] found that a diagnosis of a psychiatric disorder was not associated with functional impairment, and that while personality disorders was prevalent amongst their population (39%) they were not associated with loss of physical function or disability. However, they do report a trend toward higher physical impairment in patients with active

major depressive disorder. CFS has significant overlap and co-morbidity with psychiatric disorders, but the above studies appear to suggest that CFS is significantly distinct from psychiatric disorders, that it should be considered a separate illness and that any psychiatric comorbidity are a confounding source, and not a predictor of CFS [3].

Conclusion

CFS, neuropsychiatric complaints and neuropsychological symptoms appear to share many common features. Depressive illness and other symptomatically defined syndromes can manifest severe fatigue, somatic and psychological symptoms, which are frequently found in patients with CFS. As a behavioral response to both CFS and depressive illness, physical illness may be under the influence of disease severity and psychological factors which reflect higher than expected rates of anxiety, somatoform disorders and personality-related disorders. Depression is the predominant neuropsychiatric disorder reported among the CFS population. The precise etiological relation between CFS and depression is poorly understood, despite the vast body of recent research. Current research is however starting to lift the veil regarding shared or overlapping pathways. The IO & NS research appears to show that CFS and depressive illness share this common pathway but even though they may also share similar symptomatology, the two conditions are distinct illnesses. HPA axis data appears to show a blunted cortisol response in CFS patients that is absent in those diagnosed with depression. In contrast, there appears to be an over-activation of the HPA axis and cortisol response in depressive patients.

CFS has long been associated with neuropsychiatric complaints and neuropsychological symptoms. Depression is the key neuropsychiatric complaint reported with CFS. This close association has tended to make it difficult to differentiate between the two conditions, and some have argued that CFS is a form of atypical depressive illness. However, even though CFS and depressive illness share commonalities, evidence appears to show that both conditions have unique etiologies. Nevertheless, future studies need to explore better ways to disentangle the neuropsychiatric and neuropsychological components from the diagnostic process in CFS.

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