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COMPLEX MEDICAL-PSYCHIATRIC ISSUES (MB RIBA, SECTION EDITOR)

The Neuropsychiatric and Neuropsychological Features of Chronic Fatigue Syndrome: Revisiting the Enigma

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Abstract The aim of this article is to provide a comprehensive and updated review of the key neuropsychiatric and neuropsychological complaints associated with chronic fatigue syndrome (CFS). Neuropsychiatric and neuropsychological difficulties are common in CFS and are linked primarily to disorders of mood, affect and behaviour. The neuropsychiatric complaint most frequently encountered amongst CFS patients is depression and in particular major depressive disorder (MDD). Despite decades of research, the precise aetiological relationship between CFS and MDD remains poorly understood. This has resulted in the development of a number of interesting and polarised hypotheses regarding the aetiological nature of CFS. Recent scientific advances have however begun to unravel a number of interesting inflammatory and immunological explanations that suggest CFS and MDD are distinct yet interrelated conditions. The possibility that the overlap between CFS and MDD might be explained in terms of shared oxidative and nitrosative (IO&NS) pathways is an area of intense research interest and is reviewed in detail in this article. The overlap between CFS and MDD is further differentiated by variations in HPA axis activity between the two disorders. Important immunological differences between MDD and CFS are also reviewed with particular emphasis on antiviral RNase L pathways in CFS. In addition to the presence of neuropsychiatric complaints, CFS is also associated with neuropsychological symptoms such as impaired attention, memory and reaction time. The key neuropsychological problems reported by CFS patients are also included in the review in an effort to understand the significance of cognitive impairment in CFS.

Keywords Chronic fatigue syndrome · CFS · Depression · Generalised anxiety disorder · Neuropsychiatric · Neuropsychological · Major depressive disorder · MDD · Somatoform disorder · Personality disorder · Attention · Memory · Reaction time

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Introduction

Chronic fatigue syndrome (CFS) is a severe, systemic, acquired illness that presents with profound fatigue that is not alleviated by rest and may be exacerbated by physical or mental activity [1••]. In addition to incapacitating fatigue, CFS is also characterised by a wide range of other symptoms. These include cognitive dysfunction, sleep disturbance, myalgia, arthralgia, headache, gastrointestinal upset, sore throat and painful lymph nodes [2]. To date, no specific cause has been found and no diagnostic test for CFS exists. As such, CFS is considered to be a heterogeneous disorder that can be caused by a number of factors [3]. In the absence

of an aetiological cause, the diagnosis of CFS is made on the basis of exclusion, subjective clinical interpretation and patient self-report [4].

CFS is often accompanied by substantial physical, social and economic disability and dysfunction. Individuals with CFS typically function at significantly lower levels than their pre-CFS capabilities, resulting in considerable personal and economic morbidity [5]. The economic burdens imposed upon CFS patients tend to relate to lost or reduced employment and the costs associated with the provision of informal care [6]. Unemployment is high amongst CFS patients and is often associated with the presence of depression [7].

The absence of confirmatory physical signs or biological tests has resulted in a divisive and enduring debate as to the true aetiological nature of this illusive disorder. The genealogy of this debate is rooted in the wide range of neuropsychiatric (disorders of mood, affect and behaviour) and neuropsychological (cognitive abnormalities) features reported by CFS patients. The high rates of psychiatric and psychological dysfunction in CFS and the considerable symptom overlap with major depression have resulted in the assertion that CFS is a form of atypical depressive illness. Several studies have produced evidence that indicates significant numbers of CFS patients exhibit symptoms of psychiatric and psychological conditions [8], especially depression [9–12].

The purpose of this article is to provide a comprehensive and updated review of the key neuropsychiatric and neuropsychological complaints associated with CFS. The review builds on the work of previous authors by identifying and highlighting the most important and up-to-date developments in current scientific understanding of why neuropsychiatric and neuropsychological complaints feature so prominently in the CFS symptom complex. To that end, a comprehensive search of the relevant literature was undertaken using electronic databases (MEDLINE, EMBASE and PSYCHINFO) from January 1995 until February 2012.

The Neuropsychiatric Features of CFS

A number of neuropsychiatric complaints have been linked to CFS and relate primarily to disorders of mood, affect and behaviour. In particular, studies have shown a strong association between CFS and depressive, anxiety, somatoform and personality related disorders. Between 60 and 70 percent of CFS patients are thought to suffer from a psychiatric disorder [10], especially depressive illness. Numerous studies have demonstrated significant co-morbidity between CFS and depression and estimate that 15 to 40 percent of CFS patients suffer from major depression [9, 13, 14]. In addition to depression, anxiety disorders have been found in 20 percent of CFS patients and somatisation disorder is estimated to be present in 5 to 15 percent of CFS patients. The vast majority of the neuropsychiatric literature however is devoted to depression, as it is one of the most significant clinical problems facing CFS patients. As such, depression in CFS is discussed in considerable detail in this section, and this is followed by a brief review of the relevant aspects of anxiety, somatoform and personality related disorders in CFS.

Depressive Illness and CFS

CFS shares a number of significant overlapping symptoms with depressive illness [15]. Symptoms such as profound fatigue, sleep disturbance, poor concentration and memory difficulties are prominent features of both CFS and depression [16]. The precise relationship between CFS and depression remains unexplained and is an area of intense debate and controversy. The debate focuses on three key areas. The first one is that high rates of depressive illness are present in CFS because CFS is a form of atypical depression. The second is that high rates of depressive illness are present in CFS because of the disability imposed by the CFS disease process. Finally, the third is that high rates of depressive illness are present in CFS because CFS and depression share an aetiological pathway [17]. The absence of physical signs of disease and a known aetiological cause and the frequent and subjective nature of patients' symptoms have polarised this debate and led some researchers to argue that CFS has a psychiatric aetiology [18]. Despite the on-going debate regarding the aetiology, it is clear that CFS is a disabling condition that is associated with high rates of depression.

The prevalence of depressive illness in CFS varies widely with estimates ranging from between 21 to 27 percent [19]. More recent studies endorse these early findings with one population study noting that 22 percent of CFS patients suffer from current co-morbid depressive illness and have an overall lifetime prevalence of 65 percent [20]. Similarly, Taylor et al. [21] in a large community study found that nearly one in three patients with CFS experience clinically significant depression. Furthermore, the rates of depression in CFS appear to be much higher than those found in other chronic illnesses such as inflammatory bowel disease (16 percent), rheumatoid arthritis (15 percent) chronic back pain (20 percent) and type two diabetes (19 percent).

Major Depressive Disorder (MDD) and CFS

Major depressive disorder (MDD) is a neuropsychiatric disorder that is typified by a pathologically low mood, poor motivation, fatigue, impaired sleep and poor concentration [22]. The symptoms of MDD and CFS overlap significantly and as such it is not surprising that that the CFS literature indicates that MDD is the single most frequently occurring psychiatric disorder associated with CFS [23]. Although high rates of MDD are linked with CFS, as many as 30 to

50 percent of CFS patients do not experience psychiatric symptoms [24]. Thus, it is important to note that while MDD is a prominent feature of CFS, it affects some and not all CFS patients.

The research literature also indicates that CFS is different from MDD in a number of important symptom presentations. Johnson et al. [25] discriminated CFS patients from those with MDD using the Beck Depression Inventory (BDI). The study revealed that the CFS participants had BDI scores that related principally to physical complaints and the somatic symptoms of fatigue, while participants with MDD identified with symptoms of disturbed mood and self-reproach. Furthermore, Powell et al. [26] found significant differences between patients with CFS and patients with MDD. The CFS patients expressed fewer problems with self-esteem, guilt and suicidal ideation than the MDD group. The CFS patients were also inclined to attribute their symptoms to physical causes whereas the MDD patients experienced inward attribution. More recently, Hawk et al. [27] found that measuring the severity of post-exertional malaise, unrefreshing sleep, impaired concentration, shortness of breath and self-reproach could effectively discriminate between patients suffering from CFS and MDD.

The findings from these studies collectively indicate that while MDD and CFS share many similar symptoms (profound fatigue, pain, sleep disturbance and poor concentration) they are distinct illnesses [17, 28] and highlight that the types of symptoms expressed by CFS patients are qualitatively different. A good illustration of this point was demonstrated by Silver et al. [29] who indicated that CFS patients could be distinguished from depressive patients by measuring their response to physical exertion. The study highlighted that the CFS patients experienced an increase in fatigue post exertion, which was in contrast to the depressed patients who experienced an increase in positive mood. Furthermore, Axe [17] in a surveillance study of MDD and CFS concluded that the classic CFS symptoms of post-exertional malaise, painful lymph nodes and sore throat are not normally observed in MDD and point tentatively to a different underlying aetiology.

The Biological Basis of Symptom Overlap Between CFS and MDD

As is evident, the aetiological relationship between CFS and MDD is complex and not fully understood [30]. Despite the complexity there is an emerging body of evidence suggesting that the link between CFS and MDD might be explained through shared oxidative and nitrosative stress (IO&NS) pathways. The IO&NS pathways refer to a complex succession of biochemical reactions that result in damaging free radical and nitric oxide effects at a cellular level [16]. In one study of CFS and MDD, IO&NS was found to be responsible for damaging DNA, proteins and fatty acids and was significantly correlated to patient complaints of fatigue, muscle pain and flu-like malaise [31]. The activation of IO&NS pathways is known to give rise to fatigue and somatic symptoms [32] and can be activated by infections, psychosocial stress and immune disorders [33]. Thus, these studies indicate that CFS and MDD may share clinical manifestations of a shared IO&NS pathway.

Despite the literature indicating that CFS and MDD share key fatigue and somatic symptom clusters (probably an aberration of shared IO&NS pathways), Maes et al. [34] assert that CFS and MDD can be distinguished from each other by focusing on research evidence emerging from other biological systems. For example, MDD is classically associated with increased hypothalamus-pituitary-adrenal (HPA) axis activity and raised cortisol levels [35]. Raised cortisol is known to cause problems with verbal memory, visuo-spatial memory and executive functioning in MDD [36, 37]. By contrast, HPA studies in CFS have found reduced rather than increased cortisol levels [32]. Hypocortisolism has been consistently demonstrated in CFS and is supported by recent population-based neuroendocrine investigations [38–40]. Unlike MDD, the impaired HPA axis functioning is thought to be responsible for the symptoms of fatigue, post-exertional malaise and headaches in CFS patients [41].

Less intensively researched in CFS, but currently the focus of considerable interest, are the adrenal androgens dehydroepiandrosterone (DHEA) and its sulphated derivative, dehydroepiandrosterone-sulphate (DHEA-S). The metabolic relationship between cortisol and DHEA is an area of intense interest. This is because during psychological or physical stress there should be a shift from the production of androgens to glucocorticoids in order to maintain homeostasis [41, 42]. However, Scott et al. [43] in a preliminary study of DHEA in CFS found that the anticipated metabolic shift from DHEA to cortisol did not occur in CFS patients. The study also highlighted that CFS patients exhibited lower levels of DHEA and significantly lower levels of DHEA-S compared to patients with MDD and healthy controls [43]. Furthermore, Himmel and Seligman [44], in a small uncontrolled trial of CFS patients with low levels of DHEA, found that patients responded positively to DHEA replacement therapy.

In addition to differences in HPA axis activity between CFS and MDD, recent research has also highlighted important immunological differences. The antiviral 2-5A/RNase L pathway is one of the primary mechanisms by which interferons inhibit viral and bacterial infections [45]. Cells exposed to interferons within the system instigate the expression of genes that result in an antiviral state [45]. In recent years, a number of studies have indicated that various components of the 2-5A /RNase L pathway are both upregulated and deregulated in CFS patients compared to controls [46, 47]. Suhadolnik et al. [47], in a study

examining the immune abnormalities and status of the RNase L pathway in patients with CFS compared to patients with MDD and healthy controls, found that the CFS patients exhibited distinct RNase L abnormalities that were not present in the MDD patients or healthy controls. Similarly, De Meirleir et al. [48] found that the RNase L abnormalities were specific for CFS and extracts of peripheral blood mononuclear cells were effective at discriminating CFS patients from those with depression, fibromyalgia and healthy controls.

The studies reviewed above indicate that although CFS is often accompanied by depressive symptoms, there is evidence to support the contention that CFS is distinct from MDD. The abnormalities demonstrated in the HPA axis, DHEA and the RNase L pathways are beginning to tentatively unravel part of the CFS enigma; however further studies are required to examine these abnormalities in more detail.

CFS, Depression and Illness Limitations

CFS is associated with serious illness-imposed limitations and has resulted in some researchers asserting that depressive illness in CFS is nothing more than a natural response to the debilitating symptoms experienced by sufferers. Hickie et al. [49] produced evidence to demonstrate that the pattern of neuropsychiatric symptoms in CFS patients was similar to those observed in patients with similar medical illnesses. No evidence to suggest that CFS patients are particularly hypochondriacal was found. Thus, the study concluded that psychiatric illness is most probably a consequence of the CFS illness experience rather than something that brings about the development of the syndrome. Pepper et al. [50] came to a similar conclusion when they compared CFS patients with those suffering from multiple sclerosis (MS) and MDD. In this study, CFS patients were found to more closely resemble the MS patients than the MDD group. The study found that the CFS group experienced considerably fewer axis 1 disorders than the patients with MDD.

Additionally, Jason et al. [28] assert that CFS patients do not typically exhibit the hallmark depressive symptoms of anhedonia and worthlessness. Johnson et al. [25] examined the depressive symptom pattern in patients with clinical depression, CFS and multiple sclerosis using the Beck Depression Inventory (BDI) and found that the CFS and MS patients experienced significantly fewer symptoms of self-reproach than depressed patients. In a more recent study, Moss-Morris and Petrie [51] found that depressed controls could be distinguished from CFS patients by their low self-esteem, the inclination to make cognitive distortions across all situations and to attribute their illness to psychological factors. In contrast, the CFS patients were typified by low ratings of their current health status, a strong illness identity and external attributions for their illness. They were also more likely than depressed patients to cope with their illness by limiting stress and activity levels.

Generalised Anxiety Disorder in CFS

Anxiety disorder as defined in the DSM IV includes: panic disorder, agorophobia, generalised anxiety, social anxiety, post-traumatic stress disorder, other trauma-related reactions and anxiety due to medical conditions or substances [52]. The cardinal feature of an anxiety disorder is the occurrence of physical and/or mental aspects of anxiety that are out of proportion with the current situation and that notably influences functioning or quality of life [53].

Anxiety disorders occur frequently in the general population and have lifetime estimates of 3.5 % for panic disorder and 5.1 % for generalised anxiety disorder [54]. Fischler et al. [55] uncovered higher than expected rates of generalised anxiety disorder (GAD) in patients with CFS. GAD was characterised by an early onset and a high rate of psychiatric comorbidity, which the study authors assert indicate a predisposition to the development of CFS. Nutt [56] has highlighted that although generalised anxiety disorder is a common and serious disorder, there is no clear insight into the precise neurobiological changes principal to this condition. To date, there are few studies of neurobiological function in patients with GAD, and only limited comparative data on depression are available. Nutt [56] further argues that the relationship between CFS and GAD (reduced cerebral blood flow, sympathetic overactivity and sleep abnormalities) requires further investigation.

Somatoform Disorder in CFS

Somatisation has been defined as the inclination to describe psychological distress in the form of physical symptoms and to seek medical assistance to alleviate them [57]. Kirmayer and Robbins [58] indicate that the term somatisation encompasses a broad range of patient experiences and perceptions. These include situations in which patients describe symptoms that are entirely physical despite the presence of emotional distress, patients who are convinced they have a disease in the absence of evidence and those who persistently present to clinicians complaining of medically unexplained somatic symptoms. What is common among these three categories of somatisation behaviour is the assumption that medically unexplained patient complaints are consequent to underlying emotional distress. In addition to these three forms of somatisation, there is also a formal psychiatric diagnosis of somatisation disorder as described by DSM-III. The diagnosis of somatisation disorder is made in the presence of several years of medically unexplained

symptoms, with onset before the age of 30, together with 13 of 35 functional symptoms [59].

Studies of psychiatric illness in CFS have found very high rates of somatisation disorders [50, 60, 61]. Johnson et al. [60] in an investigation into the prevalence of somatisation disorder in CFS found that patients demonstrated a higher rate of somatisation disorder type symptoms than patients with multiple sclerosis or healthy controls. However, the study also indicated that very few of the CFS patients met the exact DSM-III-R criteria for somatisation disorder. The Johnson et al. [60] study further revealed that by changing the attribution of somatisation symptoms from psychiatric to physical (i.e. CFS symptoms were not coded as psychiatric) radically influenced the number of CFS patients diagnosed with somatisation disorder. Demitrack [62] arrived at similar conclusions, finding that when symptoms attributable to CFS were excluded, 6 of 30 patients demonstrated a lifetime history of major depression. However, when using criteria that included all symptoms, 12 of 30 patients reported a lifetime history of major depressive illness. Thus, the Johnson et al. [60] and Demitrack [62] studies demonstrate that the diagnosis of somatisation in CFS depends upon patient reports of physical symptoms and the assumption by the researcher that there is no physical cause for the symptoms.

Finally, Katon and Walker [63] assert that if CFS patients were presenting physical symptoms as a method of masking their psychological distress, then there should be an inverse association between the number of depression and anxiety symptoms and the number of reported somatic symptoms. This, however, has not been the case, with CFS patients detailing somatic, depressive and anxiety-related symptoms simultaneously [63, 64].

Personality Disorder in CFS

Research evidence indicates that personality disorder is present in as many as 39 % of CFS patients, predominantly obsessive-compulsive disorder [65]. Similar rates of personality disorder were reported in a more recent study by Cicone et al. [66]. In a study by Johnson et al. [65], 37 % of subjects with CFS met the criteria for at least one personality disorder (typically histrionic or borderline personality disorder). These studies indicate that there are higher rates of personality disorder amongst CFS patients than in non-clinical populations, which are estimated to range between nine and six percent in the general population [67]. However, these high rates of personality disorder in CFS are similar to those found in patients with other chronic medical conditions. Furthermore, some of the measures used increase the likelihood of achieving a diagnosis of personality disorder in chronically ill patients. Co-morbid depression accounted for most personality pathology in one study [65].

The Neuropsychological Features of CFS

CFS patients frequently report a variety of neuropsychological symptoms indicative of marked cognitive decline [68]. As estimated, 50 to 80 % of CFS patients complain of significant cognitive difficulties and impose considerable occupational and social morbidity on sufferers [69]. To date, neuropsychological studies in CFS have endeavoured to unravel and understand the precise nature of cognitive complaints in CFS. As such, objective evidence of cognitive disturbance has been demonstrated with deficits in attention, memory and reaction time being the most problematic for CFS patients. These three are discussed in more detail below.

Attention

The aspects of attention that have been investigated in the research literature relate to the impact of CFS on the attention span and working memory. Both of these aspects of attention are crucial cognitive functions for effective reasoning learning, and comprehension. Caseras et al. [70] in a Functional Magnetic Resonance Imaging Study of the working memory found significant differences in brain activation between CFS patients and control subjects, particularly as the demands on the working memory were increased. The study concluded that CFS patients did not engage working memory in the same way as healthy controls. The results indicated that the CFS patients had to employ additional strategies to offset their underlying cognitive problems in order to attain similar results to the control subjects. Furthermore, CFS patients displayed consistent problems with working memory in studies that required patients to concentrate over prolonged periods of time [70–74].

Memory

The memory problems associated with CFS have divided scientific opinion. Some studies have found evidence of memory difficulties in CFS [75], while others have not [76]. The conflicting findings on memory problems relate to verbal and non-verbal memory problems in CFS sufferers [69, 77]. The majority of neuropsychological studies of memory in CFS used verbal and visual memory tests. In particular, tests that assessed memory for word lists are used [78]. In terms of verbal memory, several studies demonstrate moderate to large deficits in neuropsychological tests of word list learning (e.g. Auditory Verbal Learning Test and other word list learning tasks) [73, 79, 80]. These studies concluded that immediate recall, delayed recall and recognition were impaired in CFS subjects.

DeLuca et al. [73], in a comprehensive study into the nature of memory impairment in CFS, found that CFS

patients had significant difficulty in the acquisition of verbal information. The CFS participants required considerably more attempts to learn a word list than did healthy controls. The study concluded that the memory difficulties experienced by CFS patients relate to compromises in their ability to recall verbal information. DeLuca et al. [73] suggest that these memory problems may be consequent to poor initial learning. The discrepancies in information-processing speed and working memory identified in this study may add to CFS patient difficulties with initial learning. More recently, Duffy et al. [81••] in an EEG spectral coherence analysis of patients with CFS, MDD and healthy controls found that CFS patients exhibit abnormal brain physiology that is not present in MDD or healthy controls. The study implicates bilateral temporal lobe involvement in CFS pathophysiology and is consistent with the wide-ranging memory problems reported by CFS patients.

Reaction Time

Many neuropsychological studies have measured and assessed the reaction time of CFS patients on both simple and complex information-processing tasks. The most frequently observed cognitive difficultly found in CFS relates to impairments in patient information-processing speed and efficiency [73]. Numerous studies demonstrate that CFS patients perform less well on tasks that require rapid manipulation of information and on complex and time-limited tasks than controls [79, 82]. More recently, Majer et al. [79], in a population-based study of neuropsychological performance, found that compared with controls CFS patients exhibited significant decreases in motor speed, as demonstrated by slower response times on the movement component of both the simple and choice reaction time tasks.

Furthermore, Lutgendorf et al. [83] concluded that while having controlled for depression CFS patients who experienced higher levels of cognitive difficulties also exhibited more immune abnormalities. This, they argue, is evidence to suggest that the occurrence of cognitive difficulties in CFS can be explained independently of those that typically occur with depression. Finally, Michiels and Cluydts [69] in a review of neuropsychological functioning in CFS argue that the cognitive dysfunction found in patients with CFS is unlikely to be accounted for by depression and anxiety. Daly et al. [84] came to a similar conclusion while comparing the neuropsychological function in patients with CFS, multiple sclerosis, and depression, asserting that the cognitive deficits found in CFS cannot be ascribed exclusively to the presence of depressive symptoms.

The findings from these studies indicate that CFS patients exhibit moderate to significant impairments in reaction times [69, 77]. These studies assert that that the information-processing difficulties found in CFS patients contribute to impairments noted in reaction time tasks. Moreover, fine motor speed was not impaired in persons with CFS, making it unlikely that motor functioning is predominately responsible for slower reaction times [72, 73, 79, 85].

Conclusion

This review demonstrates that neuropsychiatric and neuropsychological complaints are common amongst CFS patients. CFS is typically accompanied by higher than expected rates of depression, anxiety, somatoform and personality-related disorders. Depression, in particular MDD, is the most frequent and prominent neuropsychiatric disorder amongst CFS patients. Despite decades of research, the precise aetiological relationship between CFS and MDD remains elusive and poorly understood. However, in recent years the scientific literature has begun to unravel a number interesting inflammatory and immunological explanations that suggest CFS and MDD are distinct yet interrelated conditions.

The possibility that the overlap between CFS and MDD might be explained in terms of shared IO&NS pathways is an area of intense research interest. The IO&NS studies reviewed in this article have produced convincing evidence to support the assertion that while MDD and CFS share many similar symptoms they are distinct illnesses. This position is further strengthened in light of differences in HPA axis activity in MDD and CFS. MDD is associated with raised HPA axis activity and increased cortisol, which is in direct contrast to findings from HPA axis studies in CFS. The CFS studies have consistently reported blunted HPA axis activity and reduced cortisol. In addition to differences in HPA axis activity, recent research has also highlighted important immunological differences between MDD and CFS. Investigations of the RNase L pathway in CFS indicate that extracts of peripheral blood mononuclear cells demonstrated immune abnormalities that could effectively distinguish CFS patients from those with MDD.

Finally, this review has highlighted that, in addition to the presence of neuropsychiatric complaints, CFS is also associated with a number of neuropsychological symptoms. The key neuropsychological problems reported by CFS patients relate to cognitive deficits in respect of impaired attention, memory and reaction time. Attempts to understand the significance of cognitive impairment in CFS have in part been hampered by the overlap with MDD. Cognitive problems are core symptoms of MDD, and this has made it difficult to determine whether or not cognitive impairment in CFS is the result of the presence of MDD or is a unique aetiological feature of CFS. In light of this, this article proposes that future studies should explore cognitive impairments associated with CFS and attempt to identify if they are the same as those that typify MDD.

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