Overlap between atypical depression, seasonal affective disorder and chronic fatigue syndrome

Superposição entre depressão atípica, doença afetiva sazonal e síndrome da fadiga crônica

Mario Francisco Juruena,[1,2] Anthony James Cleare[1]

Abstract

Objective: We reviewed previous studies that have described an association between abnormal functioning of the hypothalamic-pituitary-adrenal axis and depression. In addition to melancholic depression, a spectrum of conditions may be associated with increased and prolonged activation of the hypothalamic-pituitary-adrenal axis. In contrast another group of states is characterized by hypoactivation of the stress system, rather than sustained activation, in which chronically reduced secretion of corticotropin releasing factor may result in pathological hypoarousal and an enhanced hypothalamic-pituitary-adrenal negative feedback. Patients with atypical depression, seasonal affective disorder and chronic fatigue syndrome fall in this category. Method: The literature data on the overlap between the key-words were reviewed, summarized and discussed. Results: Many studies suggest that these conditions themselves overlap biologically, showing hypofunction of central corticotropin releasing factor neuronal systems. Conclusions: Therefore, in the real world of clinical practice, patients often present in a grey area between classical idiopathic fatigue and early chronic atypical depression and/or seasonal depression. This underscores the potential common biological links underpinning commom symptom clusters not only between depression (atypical and seasonal) and chronic fatigue syndrome, but also other conditions characterized by in the hypothalamic-pituitary-adrenal axis mainly diminished the corticotropin realising factor activity.

Descriptors: Melancholic depression; Seasonal affective disorder; Fatigue syndrome, chronic; Hypothalamus-hypophyseal system; Corticotropin releasing factor

Resumo

Objetivo: Foram revisados estudos que descrevem que as alterações na função do eixo hipotálamo-pituitária-adrenal e são relacionadas com o estado psicopatológico em depressão. Além da depressão melancólica, uma série de condições podem ser associadas à hiperativação prolongada do eixo hipotálamo-pituitária-adrenal. Um outro grupo de psicopatologias é caracterizado por hipoativação do mesmo eixo com redução crônica na secreção do fator de liberação de corticotrofina. Pacientes com depressão atípica, doença afetiva sazonal e síndrome da fadiga crônica estão inclusos nesta categoria. Método: Foram revisados os dados da literatura que incluem a interseção entre estes descritores, resumidos e discutidos os principais e recentes achados. Resultados: Muitos estudos têm enfatizado que estes quadros se sobrepõem biologicamente, demonstrando hipofunção no sistema relacionado ao fator de liberação de corticotrofina. Conclusões: Na prática clínica, os pacientes frequentemente se apresentam de forma intermediária entre a fadiga e a depressão atípica crônica e/ou a depressão sazonal. Isto enfatiza o potencial biológico comum que fundamenta o grupo de sintomas não somente entre depressão (atípica e sazonal) e a síndrome da fadiga crônica e as condições caracterizadas por alterações no eixo hipotálamo-pituitária-adrenal, principalmente hipofunção e, em particular, diminuição da atividade do fator de liberação de corticotrofina.

Descritores: Depressão melancólica; Transtorno afetivo sazonal; Síndrome da fadiga crônica; Sistema hipotálamo hipofisiário; Fator de liberação de corticotrofina

[1] Department of Psychological Medicine, Section of Neurobiology of Mood Disorders, Institute of Psychiatry, King's College/University of London, UK
[2] Stress, Psychiatry and Immunology Lab (SPI-Lab), King's College/University of London, UK

Correspondence
Mario Francisco Juruena
Department of Psychological Medicine
Institute of Psychiatry, King's College/University of London
103 Denmark Hill POBox 074
SE5 8AZ London, United Kingdom
Phone: +44(0)20 78485305 Fax: +44(0)20 78480783
E-mail: M.Juruena@iop.kcl.ac.uk

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Introduction

Hormones play a critical role in the development and expression of a wide range of behaviors. One aspect of the influence of hormones on behavior is their potential contribution to the pathophysiology of psychiatric disorders and the mechanism of action of psychotropic drugs, particularly in depression. Of all endocrine axes, the hypothalamic-pituitary-adrenal (HPA) axis has been the most widely evaluated.[1-2] The HPA axis plays a fundamental role in the response to external and internal stimuli including psychological stressors. Moreover, the fundamental role of stress in precipitating episodes of psychiatric disorders in predisposed individuals is well known.[1] Abnormalities in the function of the HPA axis have been described in people experiencing psychiatric disorders. These abnormalities seem to be related to changes in the ability of circulating glucocorticoids to exert their negative feedback on the secretion of HPA hormones through binding to the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR) in HPA tissues.[3]

States associated with hyperactivation or hypoactivation of the HPA axis

Hyperactivity of the HPA axis in major depression is one of the most consistent findings in psychiatry. A significant percentage of patients with major depression have been shown to exhibit increased concentrations of cortisol (the endogenous glucocorticoid in humans) in plasma, urine and cerebrospinal fluid (CSF); an exaggerated cortisol response to adrenocorticotropic hormone (ACTH); and an enlargement of both the pituitary and adrenal glands.[2,4-5]

In general, HPA axis changes appear to be state dependent, tending to improve upon resolution of the depressive syndrome.[6] In fact, previous studies have described an impaired HPA negative feedback leading to hypercortisolemia, as in melancholic depression.[2,5-6] In addition to melancholic depression, a spectrum of other conditions may be associated with increased and prolonged activation of the HPA axis, including anorexia nervosa with or without malnutrition, obsessive-compulsive disorder, panic anxiety, chronic active alcoholism, alcohol and narcotic withdrawal, poorly controlled diabetes mellitus, and hyperthyroidism.[7] Another group of states is characterized by hypoactivation of the stress system, rather than sustained activation, in which chronically reduced secretion of corticotropin-releasing factor (CRF) may result in pathological hypoarousal and an enhanced HPA negative feedback. Patients with post-traumatic stress disorder, atypical, seasonal depression and chronic fatigue syndrome fall in this category. Similarly, patients with fibromyalgia have decreased urinary free cortisol excretion and frequently complain of fatigue. Hypothyroid patients also have clear evidence of CRF hyposecretion, see Tables 1 and 2.[3,8-11]

Since a wide variety of stressors reliably activate the HPA axis, and because glucocorticoids are the end product of HPA axis activation, these hormones have been most commonly seen as the *agents provocateurs* or even as the physical embodiment of stress-induced pathology in extreme cases. Indeed, it has been suggested that prolonged overproduction of glucocorticoids, whether as a result of ongoing stress or a genetic predisposition to HPA axis hyperactivity, damages brain structures (especially the hippocampus) essential for HPA axis restraint.[12]

Although not occurring together, both hypocortisolism and reduced responsiveness to glucocorticoids (as determined by dexamethasone challenge tests) have been reliably found.

Table 1 – States associated with hyperactivation or hypoactivation of the HPA axis

Increased HPA axis activity	Decreased HPA axis activity	Disrupted HPA axis activity
Severe chronic disease	Atypical depression	Cushing syndrome
Melancholic depression	Seasonal depression	Glucocorticoid deficiency
Anorexia nervosa	Chronic fatigue syndrome	Glucocorticoid resistance
Obsessive-compulsive disorder	Fibromyalgia	
Panic disorder	Hypothyroidism	
Chronic excessive exercise	Adrenal suppression	
Malnutrition	Post glucocorticoid therapy	
Diabetes mellitus	Asthma	
Hyperthyroidism	Posttraumatic stress disorder	
Central obesity	Nicotine withdrawal	
Childhood maltreatment	Postpartum	
Pregnancy	Allergies	
	Menopause	
	Rheumatoid arthritis	

Stress-related neuropsychiatric disorders have also been associated with immune system activation/inflammation, high central nervous system (CNS) tone, and CRF hypersecretion, which are all consistent with insufficient glucocorticoid-mediated regulation of stress hyperresponsiveness.[13] We define insufficient glucocorticoid signaling as any state in which the signaling capacity of glucocorticoids is inadequate to restrain relevant stress-responsive systems, either as a result of decreased hormone bioavailability (e.g., hypocortisolism) or as a result of attenuated glucocorticoid responsiveness (e.g., secondary to reduced glucocorticoid receptor sensitivity). Thus defined, insufficient glucocorticoid signaling implies no specific mechanism or absolute deficiency, but focuses on the end point of glucocorticoid activity instead. The fundamental question is whether the glucocorticoid message is getting through in a manner adequate to the environment (external and internal) in which an organism finds itself.[14]

Melancholic vs. atypical

There is increasing data on the fact that depressive disorders include a group of disorders, which can be different with regard to HPA axis activity, immune functions, and treatment response.[3,14-16] Depression is a heterogeneous illness, and two of its subtypes are melancholic depression and atypical depression, see details on Table 1.

Melancholia constitutes a strong historical description of one of them, with well-defined limits and homogeneous content. 'Non-melancholia', as a description of the other depression,

Table 2 – Corticosteroids and stress-related disorders

HPA dysregulation	
Enhanced feedback	Feedback resistance
Reduced CRF function	Enhanced CRF function
Reduced adrenocortical sensitivity	**Enhanced adrenocortical sensitivity**
Vulnerability to disease	
Atypical depression	Melancholic depression
Seasonal affective disorder	
Chronic fatigue syndrome	
Fibromyalgia	
Susceptibility to inflammation	Susceptibility to infection

is problematical because it defines a group by what it is not. In fact, non-melancholia is a mixture of dysphoria, anxiety, and depressive character.[17] According to some authors, in the next edition of DSM (DSM-V), the term major depression will be rearranged: melancholic mood disorder (MMD), and nonmelancholic mood disorder (NMMD) may become two of the main entities in the mood disorder section.[18] Nevertheless, it should be highlighted that many patients with depression do not fully match either of these classifications. About 15-30% of patients with major depression present with an atypical episode and 25-30% with a melancholic type.[3,19]

Melancholic depression is distinguished by loss of appetite and sleep; melancholic patients are usually anxious and lose responsiveness to the environment. Those with melancholic depression tend to feel worse in the morning and those with atypical depression worse in the evening. Chrousos and Gold have suggested the hypothesis that continuous stress system dysfunction, characterized by either hyper- or hypoactivity of the HPA axis, play a role in various pathophysiological conditions, including a range of psychiatric, endocrine and inflammatory diseases.[20]

While the debate concerning the best clinical criteria for atypical depression continues, the existing data propose that the neuroendocrine pathophysiology is different and even opposite to that observed in patients with melancholic depression.[3,16,20] It is recognized that HPA axis overdrive and hypernoradrenergic function are related to melancholic depression, with elevated plasma cortisol levels and some evidence for a strong CRF drive. On the other hand, there is increasing data showing that hypoactivity of the HPA axis, less CRF and possibly lower than normal cortisol production, and reduce activation of noradrenergic pathways are present in patients with atypical features of depression.[3]

This almost complete opposite neuroendocrine disorder, with reduced HPA activity and CRF secretion, mediated by an increased negative feedback by cortisol and hyponoradrenergic function, was first described more than 15 years ago in atypical depression,[20] and several studies have since substantiated the evidence for HPA hypofunction in this subgroup of depressed patients.[21-23] While those with melancholic depression fail to suppress cortisol release after dexamethasone, those with atypical depression have an increased suppression of cortisol.[23-24]

In addition to HPA axis activity, different alterations of the serotonergic system may also play a significant function in the melancholic and atypical phenotypes. Thus, the melancholic subtype with noradrenergic and HPA axis overdrive seems to be associated with reduced 5-HT_{1A} autoreceptor function and, therefore, enhanced serotonergic activation of the HPA axis, as well as an acute phase immune reaction. The latter contributes to HPA axis stimulation and reduces negative feedback inhibition by corticosteroid receptors. The resulting hypercortisolism can further impair 5-HT_{1A} receptor functions, leading to a vicious circle, which may not be effectively resolved by most selective serotonin reuptake inhibitors (SSRI).[7,25] On the other hand, patients with atypical depression and low HPA activity seem to have reduced noradrenergic and serotonergic afferent stimulation, possibly due to reduced serotonin (5-HT) synthesis and, unlike melancholic patients, an unimpaired 5-HT_{1A} autoreceptor function.[3,25]

Table 3 – Clinical differences between melancholic and atypical depression

	Melancholic	Atypical
Symptoms		
Level of arousal	Hyperaroused	Hypoaroused, apathetic
Anxiety level	Anxious	Generally not anxious
Reactivity	Relatively unreactive to environment	Reactive to environment
Emotional memory	Predominance of painful emotional memory	Relatively out of touch with past
Cognition	Decreased concentration, perseveration	Loss of focus
Behavior	Shifts to relatively well-rehearsed behaviors	Unmotivated, inactive
Strong link to Bipolar II	No	Yes
Neurovegetative		
Sleep	Decreased sleep, poor quality	Increased sleep, poor quality
Appetite	Decreased food intake, weight loss	Increased food intake, weight gain
Energy level	Overt energy level variable	Marked lethargy and fatigue
Libido	Diminished	Diminished
Diurnal variation	Worse in morning	Worse in evening
Neuroendocrine		
HPA axis	Centrally activated	Centrally-mediated hypoactivity
Cortisol output	High	Low
CRF	High	Low
Dexamethasone suppression test	Low suppression	High suppression
Response to prednisone	-	Yes
Autonomic		
Sympathetic activity	Increased	Decreased
Body composition		
Body Mass Index (BMI)	Normal	High
Lean body mass	Decreased (sarcopenia)	Normal
Total body fat	Normal or increased	Increased
Immune function	Relatively immunosuppressed	Relatively immunoenhanced
Medical sequelae		
Heart disease	Premature ischemic heart disease	Premature ischemic heart disease
Osteoporosis	Premature osteoporosis	Normal bone
Infection/inflammation	Increased susceptibility to infection	Increased susceptibility to inflammation
Neurodegeneration	Hippocampus/medial prefrontal cortex	?

Adapted from [18,24]

Table 4 – Definitions for atypical features based on recent studies. May better differentiate atypical depression from melancholia and undifferentiated depression

Atypical depression/depression with atypical features – Interchangeable terms referring to the depressive group defined by the DSM-IV criteria for depression with atypical features	
Early/chronic atypical – The subset of atypical depression with (all required)	a. Age of onset of significant dysphoric symptoms prior to age 20 b. Dysphoric symptoms for at least 2 years c. No spontaneous well-being longer than 2 months since depression onset
Lateonset-chronic atypical – The subset of atypical depression with (either)	a. Illness duration > 2 years b. Spontaneous well-being at least 2 months c. First dysphoric symptoms arise after age 20
Probable atypical depression	a. Significant mood reactivity b. One associated feature from among - Hyperphagia - Hypersomnia - Extreme leaden paralysis - Chronic interpersonal rejection sensitivity c. Does not meet criteria for melancholic or catatonic features
Melancholia/depression with melancholic features – Interchangeable terms referring to the depressive group defined by the DSM-III criteria for depression with melancholic features	
Undifferentiated depression – Depression with neither atypical nor melancholic features	

Adapted from [3,30-33]

The debate regarding the best clinical criteria for atypical depression continues

Early British experience with monoamine inhibitors (MAOIs) at St. Thomas's Hospital in London has generated the concept of a depressive subtype "somewhat atypical states, sometimes resembling anxiety hysteria with secondary depression" that differs from the endogenous depression that responds to tricyclic antidepressants and electroconvulsive therapy (ECT).[27-28] West and Dally did not identified current DSM-IV criteria for the atypical features specifier, such as hypersomnia and hyperphagia, although "fatigue" was commonly reported.[27-29] The term atypical depression was adopted, although not clearly defined. Later, Klein and Davis described a subgroup of atypical depression which they labeled "Hysteroid dysphoria", reflecting the tendency of patients to idealize romantic relationships, to be euphoric in love but overcome when rejected, and typically to overeat and oversleep.[30]

Thus atypical depression has been used in the past to mean a number of different conditions, including non-endogenous depression, depression secondary to another condition, depression associated with anxiety or panic, and depression with reversed biological features.[20,29-31] However, as the concept has evolved, atypicality has been more tightly defined within rubric of DSM-IV.

In general, patients with thus atypical depression tend to have an earlier onset, a higher proportion of females, increased comorbidity with dysthymia, substance misuse and sociopathy, and there is a higher incidence of atypical depression among their relatives. Sullivan et al.[32] have used data from the large US National Comorbidity Survey and, by means of latent class analysis, they have identified six syndromes, two of which correspond to mild atypical depression and severe atypical depression, respectively. Atypicality was associated with decreased syndrome consequences, comorbid conduct disorder and social phobia, higher interpersonal dependency and lower self-esteem, and parental alcohol/drug use disorder. This study has confirmed earlier epidemiological findings from other samples regarding the validity of the atypical depression concept. For example, a study of 1,000 female twin pairs has suggested that there is a syndrome of atypical depression characterized by increased eating, hypersomnia, frequent, relatively short episodes, and a proclivity to obesity.[32] Furthermore, individuals with recurrent episodes tended to have the same syndrome on each occasion and members of twin pairs concordant for depression had the same depressive syndrome more often than expected by chance with resemblance greater in monozygotic than in dizygotic pairs.[33]

The assessment scale developed by the Columbia group is the most widely used. The Atypical Depression Diagnostic Scale (ADDS)[30] categorizes patients into one of three categories: *definite atypical depression* (mood reactivity preserved > 50%, 2 positive symptoms [hyperphagia, hypersomnia, severe fatigue, leaden paralysis, rejection sensitivity]); *probable atypical depression* (mood reactivity preserved > 50%, 1 positive symptom); or *simple mood reactive depression* (mood reactivity > 50%, no additional symptoms).

The literature subsequent to publication of the DSM-IV largely supports the validity of depression with atypical features, as distinct from melancholia and depression with neither atypical nor melancholic features.[16,19,26,32-34] However, recent reports have also suggested that changes should be considered for DSM-V's criteria for atypical features to produce a pathophysiologically more homogeneous group than do the DSM-IV criteria. Increased homogeneity may amplify the course of illness criteria and loosen the criteria for associated features. These changes in the criteria for atypical features may better differentiate atypical depression from melancholia and undifferentiated depression (see Table 4 for definitions).[3,30-33]

Gold et al. have suggested that, while typical major depression (melancholic) can be characterized by an excessive activation of the physiological stress systems, the locus ceruleus-noradrenergic system, and the hypothalamic-pituitary-adrenal axis, opposite changes are present in atypical depression.[36] Some support for this is provided by studies showing that the control of noradrenergic function is relatively preserved in atypical compared to typical depression.[21-22] Gold et al. have suggest that diminished CRF activity is specifically related to the hypoarousal symptoms (hypersomnia, hyperphagia, lethargy, fatigue, and relative apathy) of the syndrome.[37] Evidence supporting the fact that

low CRF rather than low cortisol is related to the atypicality syndrome comes from one detailed study of Cushing's syndrome patients. In this syndrome, cortisol is high and CRF low. Dorn et al. have found that atypical depression was the predominant depressive syndrome, affecting 17 out of 33 Cushing's syndrome patients.[38]

Stewart et al. have indicated two discernable groups within DSM-IV depression with atypical features.[35] These include late onset, non-chronic course, positive imipramine response, left hemisphere perceptual processing bias, hyperactive HPA axis, and less chronic and less atypical depression in family members. Regarding early/chronic atypical, late/non-chronic atypical had significantly higher afternoon cortisol and postdexamethasone cortisol, and showed a trend toward a more blunted cortisol response to dextroamphetamine. In each test of HPA axis function, late/non-chronic atypical appeared to have findings more similar to those expected in patients with melancholia than to early/chronic atypical.[35] The group that is defined by the early onset of a very chronic illness does not respond to imipramine, has a relative right hemisphere perceptual processing bias, a hypoactive HPA axis, and family members who are more likely to have chronic and/or atypical depression, see Table 4. These results suggest changes in the DSM-V criteria for depression with atypical features.[36] The Columbia group has suggested amending the DSM-IV criteria for atypical features to exclude the later onset and less chronically depressed patients, see Table 5.

Seasonal affective disorders (SAD)

Rosenthal et al., pioneers in SAD research, have described SAD as "an energy crisis".[39] SAD is described by recurrent affective episodes in temporal relationship with a particular period of the year, and it tends to run in families and is heritable as evidenced by studies with twins.[40] Most patients with SAD experience atypical symptoms including increased need for sleep, carbohydrate craving with increased appetite and weight, and extreme fatigue. The opposite is not true, only about 10% of the patients with atypical depression have a seasonal pattern, but although the relationship between atypical depression and seasonal depression is very close, a small trial of light therapy in atypical depression had no effect at all.[41]

Higher incidences of SAD are reported in latitudes where there are significant decreases in the hours of daylight in fall/winter periods. For example, the incidence of SAD in latitudes of 45-50° or higher is over 10% compared to latitudes lower than 30°, where the prevalence is around 1%.[42] As in atypical depression of those who have SAD, 60% to 90% are women, and it occurs more frequently in younger people, often beginning when the person is at his/her twenties.[43] Many of the symptoms of winter depression (e.g. hypersomnia and hyperphagia) are known to be regulated by hypothalamic 5-HT. Thus, patients with SAD are thought to be abnormally vulnerable to the decreases in hypothalamic 5-HT that normally occur during the winter.[44-45]

There is an opposite form of seasonal affective disorder in which individuals regularly become depressed in the summer.[46] In some respects, the behavioral symptoms of summer depression tend to be opposite to those of winter depression. For example, individuals may sleep less and lose weight when they are depressed in the summer. Also, there is some evidence that heat induces summer depression, quite important in this time of global warming and in some tropical countries. However, recurrent summer depression in tropical areas and its possible causes have been studied much less extensively than winter depression.[46-48]

The etiology and pathophysiology of SAD is not fully understood yet, although hypotheses exist that relate the condition to period of sunlight, changes in the circadian cycle and, subsequently, the secretion of melatonin. The pineal gland responds to darkness by secreting melatonin, which resets the brain's central clock and helps the light/dark cycle reset the sleep/wake cycle and other daily rhythms. Circadian pacemaker regulates seasonal changes in behavior by transmitting a signal of day duration to the other parts of the organism.[44-46] The signal is expressed equally in the period of nocturnal melatonin secretion, which is longer in winter than in summer. The length of nocturnal melatonin secretion is programmed by processes that happen in the cells of the suprachiasmatic nucleus (SCN) of the hypothalamus. As the length of the night changes, the SCN makes adjustments in the period of melatonin secretion so that it becomes longer in winter and shorter in summer. Melatonin receptors in the posterior hypothalamus and pituitary mediate most of these responses.[49] Lewy et al. have found associations between depression ratings and circadian period. They have revealed a therapeutic window for most favorable configuration of circadian rhythms and how these rhythms can be reset by taking melatonin supplements at the right time of the day.[49]

It has been suggested that seasonal effects on mood and behavior (seasonality) are related to changes in serotonergic and hypothalamic-pituitary-adrenal (HPA) functions.[50] A placebo-controlled study of hormonal responses after administration of the serotonin-releasing agent fenfluramine has found that patients with winter SAD had weaker cortisol and prolactin responses than healthy people.[51] Baseline cortisol levels were significantly higher in the Spring/Fall group compared to the Winter/Summer group. The Spring/Fall group and the Winter/Summer group may represent different subtypes of major depression.[52]

Table 5 – Proposed DSM-V criteria for depression with atypical features

1. Meets criteria for major depression or dysthymia
2. Significant mood reactivity when depressed
3. Associated features (one required)
a. Hyperphagia
b. Hypersomnia
c. Leaden paralysis
d. Pathologic rejection sensitivity
4. Onset of significant dysphoria prior to age 20
5. No spontaneous well-being (i.e. > 2 months) since onset
6. Illness lasting at least 2 years
7. Does not meet criteria for melancholic or catatonic features
8. Syndrome is not better explained by a medical disorder and is not substance-induced
9. Psychosis is not present

Adapted from [27]

Chronic fatigue syndrome

Patients complaining of fatigue are common. Between 20% and 50% of the population report suffering from fatigue (depending on the definition), while 10% of primary health care patients have 6-month or longer fatigue.[53] A smaller group can be shown to have significant disability resulting from their fatigue.

Chronic Fatigue Syndrome (CFS, popularly known as myalgic encephalomyelitis) is a disorder characterized by profound disabling chronic fatigue in association with a number of other

symptoms. Fatigue must be severe enough to cause a significant loss of physical and social function for a minimum of 6 months, and 4 of the following symptoms must also be present: sleep disturbance (usually hypersomnia), concentration impairment, muscle pain, multi-joint pains, headaches, post-exertional exacerbation of fatigue, sore throat, and tender lymph nodes.[54] Exclusions include a clear underlying organic cause and severe psychiatric disorder such as psychotic depression. Studies estimate that its prevalence in the community varies from 0.5% to 1.5%.[53]

The etiology of CFS however remains elusive, with the likely outcome that it is a heterogeneous condition with a multifactorial etiology. Recent studies have suggested that there is a genetic propensity to suffer from chronic fatigue, with the concordance between monozygotic twins more than twice that of dizygotic twins.[55] Multivariate modeling suggests that part of this vulnerability is conferred through the genetic tendency to suffer from anxiety or depression, but that part is independent of psychiatric disorder.[55]

Most patients in whom CFS is diagnosed date the onset of their symptoms to a viral infection, such as an upper respiratory tract infection or influenza. This led initially to great efforts to find the virus responsible for CFS, with the assumption that CFS was due to a persistent viral infection. However, research in patients diagnosed with specific severe viral infections has shown that some viruses are more likely to result in chronic fatigue than others and some patients are more vulnerable than others. Thus whilst 25% of patients develop chronic fatigue after viral meningitis, the risk is five-fold higher in those with a previous psychiatric disorder and those who make a convalescence from illness (involving bed rest and/or time off work).[56]

Although muscle pain and complaints of muscle fatigability are common, there is little objective evidence that these symptoms have a primary neuromuscular origin. Most tests of neurophysiological function have shown normal results, particularly once the secondary effects of inactivity are taken into account. There may be a small group whose symptoms are related to primary muscle dysfunction, but given the importance of mental fatigue and fatigability, central rather than peripheral explanations are more likely to be relevant for most patients.[53]

The HPA axis is the primary long-term mediator of the body's stress response. Initial interest in this axis was generated by the observation that Addison's disease (primary adrenal gland hypofunction), like CFS, produces fatigue, myalgia, arthralgia, sleep and mood disturbance. Recent research has revealed largely consistent findings of mild hypocortisolism in CFS sufferers including reduced plasma cortisol, reduced 24-hour urinary free cortisol output, and reduced salivary cortisol. The exact site of any disturbance in the axis is not yet clear: whilst some data point towards a hypothalamic dysfunction, other data are compatible with reduced adrenal gland function.[57] Many factors influence cortisol secretion, including changes in sleep, activity and appetite. Night shift working produce similar HPA axis changes to those seen in CFS, suggesting that they may be a consequence rather than a cause of CFS.[57]

Although there are several reports of alterations in immune parameters, most frequently of a mild immune activation, these are certainly not consistent. They may also be secondary to the decreased cortisol tone or mood disorder. Furthermore, some large studies have failed to find evidence of any immune dysfunction or, alternatively, that it is restricted to a subgroup.[53] It has been suggested that CFS is an immunological disorder with secondary evidence of viral reactivation or, on the other hand, that the immunological findings reflect a hyperactive immune system secondary to viral infection. A third view is that all the observed changes are simply epiphenomena of abnormal psychological states, or there is even the opinion that no reliable immunological changes occur at all. What may be important for clinicians is that most studies have found no link between immune and clinical parameters, either for current symptoms or for outcome, although there are exceptions. Likewise, although abnormal cytokine release in response to antigen challenge is a tempting model for CFS, this would have to be centrally mediated, and has not been proven.[53]

Changes in central neurotransmitters have been hypothesized as a possible underlying mechanism for increased central fatigue. 5-HT has been the most studied after early findings that post-exercise fatigue was associated with an increase in plasma tryptophan and, through the normal metabolic pathways, increased synthesis of 5-HT in the brain. In CFS, similar findings have emerged.[58] Increased levels of the 5-HT metabolite 5-HIAA have been found in cerebrospinal fluid (CSF) and plasma of CFS patients compared to healthy controls, suggesting increased turnover of 5-HT. Further studies have directly investigated central 5-HT function in CFS patients using the neuropharmacological challenge paradigm. For example, the prolactin response to a standardized dose of d-fenfluramine, a drug that selectively causes release of 5-HT from the raphe nuclei neurons, gives some indication of the responsiveness of brain 5-HT pathways. CFS subjects show a higher prolactin response than controls, in contrast to depressed patients who have a reduced response.[58]

It is possible these chances are of physiological significance, since 5-HT is known to be important in the physiological control of sleep, appetite and mood. In parallel with the opposite 5-HT changes, these features are disturbed in opposite directions in classic endogenous depression (insomnia, anorexia, agitation) and CFS (hypersomnia, hyperphagia and retardation). Given our knowledge of brain physiology, it is also possible that these are secondary to low cortisol levels or the effects of inactivity, sleep disturbance or disrupted circadian rhythms.

There have been several recent studies using neuroimaging techniques such as single photon emission tomography (SPET) to study cerebral blood flow in CFS. Whilst a number of abnormalities have been found, including lowered perfusion of the brain stem and frontal lobes, many investigators have failed to replicate these findings. However, studies in progress are just beginning to identify the neural correlates of the symptom of fatigue; these may enhance our understanding of the brain mechanisms underlying the sense of effort.[59]

Discussion

In the literature and the classification systems, the appearance is often given of hard and fast divide between depression (melancholic, atypical and seasonal) and CFS. In the real world of clinical practice, patients often present in a grey area between classical idiopathic fatigue and early chronic atypical depression and/or seasonal depression. Indeed, many researchers are now suggesting that the conditions themselves overlap biologically, with the existence of disease spectrums rather than discrete categories. For example, Gold et al. have suggested that there is a biological overlap between several conditions (CFS, atypical depression, seasonal affective

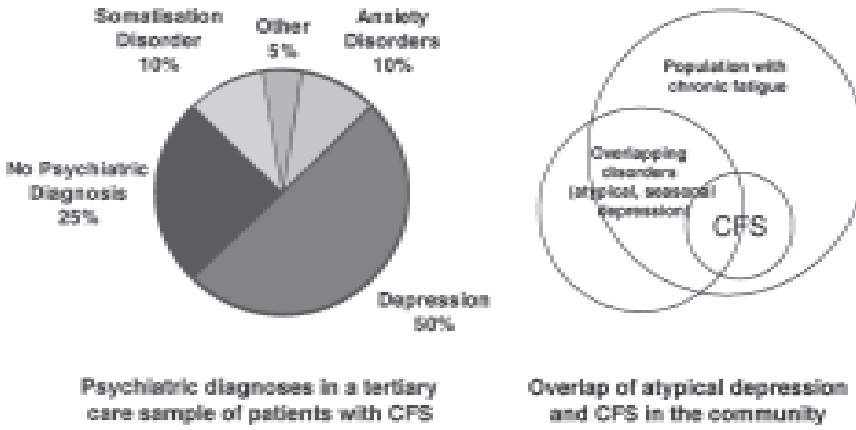

Figure 1 - Psychiatric Disorder in CFS

disorder, hyperimmune states, etc.) in which fatigue and other related symptoms are present, all of which show hypofunction of central CRF neuronal systems.[37] The concept of affective spectrum disorder likewise gains in popularity, linking not only depression, atypical depression and CFS but also other disorders in which abnormalities of mood are common, and abnormalities of 5-HT metabolism often suspected. Simply using existing diagnostic criteria for depression in CFS leads to rates of depression of around 50%. Figure 1 shows the results of one such study.[60] and a conceptualization of the overlap based on the scheme by Fukuda et al.[54]

When it comes to treatment, it is our impression that a rigid adherence to formal classificatory systems is rarely productive. Instead, a pragmatic, multidimensional approach seems to be the best choice. Likewise, what has become known as "stepped care" also provides a conceptual framework for approaching patients, in which clinicians commence with simple, straightforward approaches, usually taking place in primary care, and gradually involve more complex treatment modalities when or if patients fail to respond. Therefore, we suggest that management decisions are based on the results of a multidimensional assessment in which all relevant factors contributing to symptoms are assessed and treated appropriately. Clearly, one must always remeber to consider the importance of mood disorder in each and every patient presenting with unexplained fatigue. However, that is only one part of a broad assessment. Finally, any treatment plan must take great account of the patient's own views as to etiology – if a patient clearly fulfils criteria for depression, atypical or typical, but equally clearly does not accept that mood plays a role in his or her symptoms, then a bland prescription of antidepressants is not likely to be well received or adhered to.

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