

Atypical depression as a secondary symptom in chronic fatigue syndrome

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Summary Chronic fatigue syndrome (CFS) has gained prominence since 1988 and a substantial amount of research has been done in this domain. However, it is still regarded as a controversial condition. Moreover, most of the symptoms of CFS itself are non-specific, occurring in many illnesses; some of the symptoms are also common in depression. Indeed, an area of continued controversy and debate involves the diagnostic overlap between CFS and psychiatric disorders. Through anecdotal evidence, atypical depression appears to be common in CFS. Recent developments in psychobiology underscore the role of the acute phase response and its associated sickness behavior in affective disorders. Thus, we hypothesize that atypical depression is sickness behavior rather than an affective disorder as shown by anecdotal evidence in CFS.

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INTRODUCTION

Physicians have been confronted with the complaint of fatigue since the inception of the doctor–patient relationship. In the majority of cases, fatigue, like the remainder of its symptomatic counterparts, resolves once patients are cured of their clinical illness. In contrast, sometimes, a person will suffer from persistent exhaustion so profound that this symptom, instead of the initiating disease, dominates the clinical picture (1). This is the situation in chronic fatigue syndrome (CFS), an illness that has gained prominence since 1988, when its name was first coined and a working case definition was established by the Centers for Disease Control and Prevention (2).

CFS continues to be regarded as a controversial condition, particularly with regard to competing claims concerning etiology and treatment. Recently, more

evidence underscores the immunopathology of CFS (3). There is little disagreement about what constitutes the classic presentation of this syndrome and the usual demographic features of CFS sufferers (4–8). Moreover, all of the symptoms are non-specific, occurring in many illnesses, and some of the symptoms – disrupted sleep, difficulty with memory and concentration, myalgias, and fatigue itself – are common in clinical depression.

Indeed, an area of continued controversy and debate involves the diagnostic overlap between CFS and psychiatric disorders. Patients (50–70%) with CFS fulfill the operational criteria for a psychiatric disorder: most often depression, followed by anxiety and somatization disorder (9–13). Most research has found that 25–50% of CFS patients have had psychiatric challenges, such as major depression prior to the onset of their illness (9,10,14).

DEPRESSION

Researchers who have studied infection and immune activation in animals (15) as well as in humans (Maes et al., 2001; 1999) have often described the behavioral

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state observed during disease states such as depression or depressed mood. Furthermore, the behavioral sequelae of immune activation also known as the acute phase response, resemble the characteristics of depression. The essential features of depression as described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (4th ed.; American Psychiatric Association, 1994) are depressed mood and the loss of interest in, or the pleasure derived from, most of the individual's usual activities (anhedonia). To be diagnosed as depressed, an individual must also exhibit at least five of a cluster of symptoms: (a) disturbance in appetite or weight loss, (b) psychomotor disturbance, (c) sleep disturbances, (d) fatigue or loss of energy, (e) difficulty in thinking or maintaining attention, (f) thoughts of suicide or attempts at suicide, and (g) feelings of worthlessness or excessive guilt.

In a large group of individuals with CFS attending our clinic, it appears that atypical depression is one of the most common affective disorders in CFS patients. Atypical depression is diagnosed when a person with depressive symptoms feels better when confronted with a positive event. Furthermore, they need to have at least two of the following symptoms: significant increase in weight, hypersomnia, exhausting fatigue and hypersensitivity towards other persons, which results in social limitations (DSM-IV, 4th ed.; American Psychiatric Association, 1994) and diurnal variation of depression that is at its best in the morning (16). An atypical depression can follow a dysthymic episode or can occur after a major depression. Studies of depressed outpatient populations have found rates of definite or probable atypical depression ranging from 13% to 36%, depending on the definition of atypicality used (17–19). Patients with atypical depression report a higher number of self-reported symptoms, greater impairments in functioning, and higher rates of chronic dysphoria than patients without atypical depression (20).

Recent developments in the psychobiology of stress and affective disorders document that both the experience of stressful life events and the syndrome of depression can be associated with alterations in immune function. In general, psychological states have been hypothesized to mediate alterations in cell-mediated immune function, i.e., natural killer (NK) cell activity (21). However, the association between depressive symptoms and altered immune parameters does not necessarily imply a potential affective disorder as shown by Irwin et al. (21). They compared patients with an affective disorder (depression) with individuals who experienced a severe life event or major difficulty. As a result, individuals who underwent a major life event, showed a reduction in natural killer cell cytotoxicity

even though they did not show any of the pathological depressive symptoms.

IMMUNOLOGY

The specificity of immunity entails a cost – a large number of cell divisions are needed to generate enough cells with the required receptor before an effective response can be mounted. Each cell cycle requires 8–12 h. Therefore, *innate immunity* is needed when cells are confronted with bacteria or viruses. For instance, macrophages contain enzymes that can kill foreign cells by engulfing, and thus destroying, them directly. In addition, macrophages become activated and synthesize and release a number of products that function in defense, e.g., nitric oxide. Activated macrophages also synthesize and release the pro-inflammatory cytokines, interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α). IL-1 is the most potent cytokine with regard to initiating immune responses mediated by the brain. Indeed, blocking IL-1 blunts much of the sickness reaction to infection, while administering IL-1 peripherally produces most of the reaction. In CFS, increased levels of cytokines have been reported by several researchers (22). Moreover, an increased level of RNase L ratio is found in CFS, which is consistent with a decreased level of TNF- α (3,23). In addition to their local actions, the pro-inflammatory cytokines orchestrate a complex set of widespread changes throughout the entire organism that also function to combat infection and injury. This global reaction to infection or injury is often called the acute phase response (24) or illness and is associated with illness *behavior*. Here, illness behavior refers to the coordinated set of behavioral changes that develop in ill individuals during the course of an infection. At the molecular level, these changes are due to the effects of pro-inflammatory cytokines in the brain. At the behavioral level, illness behavior appears to be the expression of a central motivational state that reorganizes an organism's priorities to cope with infectious pathogens (15). This constellation of non-specific symptoms include fever, weakness, malaise, listlessness, inability to concentrate, depression and lethargic symptoms. Thus, these symptoms of sickness are not pathological or a sign of debilitation, but rather a defensive response that evolved long before medicine to control infectious agents.

HYPOTHESIS

We argue that a variety of behavioral, affective, and cognitive phenomena are driven by events in the immune system in CFS patients. Moreover, we argue that

atypical depression is not an affective disorder but a symptom constellation called sickness behavior or the acute phase response.

ATYPICAL DEPRESSION AS A SYMPTOM CONSTELLATION OF ILLNESS BEHAVIOUR

Several studies have demonstrated that a single administration of a substance that activates macrophages also releases cytokines and therefore activates the immune-to-brain circuit under discussion here. It produces anhedonia, which is reversed by antidepressant drugs (25).

It should also be noted that atypical depression is often associated with a deregulation of the hypothalamic–pituitary–adrenocortical (HPA) axis characterized by increases in basal levels of adrenal glucocorticoids and a reduced potency of dexamethasone to suppress adrenal glucocorticoids (16). This HPA axis deregulation is also reported in CFS patients (26). Moreover, a single administration of IL-1 can produce long-lasting changes in the HPA axis (27). Furthermore, the animal literature strongly supports the contention that immune activation and the pro-inflammatory cytokines induce a state that is ‘depressive-like’. A number of investigators have studied the psychological changes that occur during and following infectious diseases. Infectious diseases obviously involve immune activation and cytokine release. Depression has been the most consistently reported psychological disturbance in infectious diseases. Interestingly, Yimiya (25) found that vaccination for rubella produces an increase in depressive symptomatology two weeks after administration of the vaccine, a time during which immune response to the vaccine should be high. Finally, depressed mood has frequently been observed as a consequence of cytokine administration to humans.

Thus, depression does appear to be associated with the activation of innate immunity; just as is stress. Perhaps the essential feature of atypical depression is a decrease in energy usage during periods of sickness or injury to promote subsequent recuperation. The notion is that it would be adaptive to conserve energy during threats beyond the organism’s ability to cope, thus serving an important function for survival.

Whatever causes depression may also activate the same neural responses that evolved to mediate sickness and activate the sickness response circuitry. Some of the symptoms of depression, particularly the vegetative symptoms, may therefore be the result of this process and represent essentially sickness responses. Similarly, depression may result from deregulation of the mechanisms involved in these neural responses, whether by genetic or acquired mechanisms.

The main critical point seems to be that illness behavior is characterized by ‘anorexia’ and ‘weight loss’,

whereas atypical depression seems characterized by ‘increased appetite’ and ‘weight gain’. When looking closer at the diagnostic criteria of atypical depression, it appears that only two of four characteristics are needed. One of these four characteristics is ‘weight gain’ or ‘increased appetite’. Moreover, these two criteria are included in the Diagnostic and Statistical Manual of Mental Disorders, meaning that a percentage of the subjects used to establish these characteristics of depression showed ‘weight gain’ and/or ‘increased appetite’. However, other subjects used in this statistical analysis may have presented with ‘anorexia’ and/or ‘weight loss’.

TESTING THE HYPOTHESIS

Testing this hypothesis poses a difficult problem, because both depressive disorders and endocrine function can alter immunologic challenges. More research is needed to reveal all the complex interactions and features. Furthermore, when one considers that cytokine production and HPA axis function are dynamic, rather than static, it is not surprising that the precise nature of their interactions may vary enormously. Thorough immunological studies in subjects with atypical depressions and CFS will be necessary to confirm our hypothesis.

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