Holistic Performance Institute Position Stand: Adrenal Fatigue

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Abstract

Adrenal fatigue is a common diagnosis amongst alternative and complementary medicine practitioners but its diagnostic criteria, aetiology, scientific rationale and treatment methods are not well described in the literature. A review of the relevant literature was conducted to formulate a position statement for clinical practice on the topic of adrenal fatigue.

This review shows that the diagnostic criteria are likely to provide a finding of adrenal fatigue in most clients due to the large number of signs, symptoms and comorbidities suggested as being a part of the complex of adrenal fatigue. These signs and symptoms are not however suggestive of defined hypoadrenia and a diagnosis of adrenal fatigue is therefore problematic. There are significant variations in individual characteristics of fatigue. While there may be some hypothalamo-pituitary axis and biochemical dysfunction present, overall baseline and total cortisol levels do not appear to be significantly different between those with CFS and controls. There may be subtle and individual-dependent differences in cortisol response, and metabolism and clearance. However, the causative, corollary or resultant nature of these and other findings are yet to be properly elucidated.

The position of the Holistic Performance Institute is that until there can be proper reliability and validity testing of adrenal fatigue questionnaires, and a definitive and validated diagnostic protocol for the condition, the diagnosis of ‘adrenal fatigue’ should be avoided. We further caution that this diagnosis by alternative practitioners who may not be qualified and registered should be avoided, and that misleading diagnoses may put patients at risk due to the non-detection of other conditions.
Introduction

Fatigue is a common presenting symptom of clients and patients seeking treatment through orthodox and complementary avenues.

Adrenal fatigue syndrome (AFS) is a common diagnosis in the natural and complementary health fields. It has been stated that around 80% of people in the western world will suffer from ‘Adrenal Fatigue’ however, this contention lacks supporting evidence and better-defined and accepted disorders characterised by fatigue, which might indicate true population prevalence of AFS show a much lower prevalence. For example, fibromyalgia in the general population affects around 2% of people and fewer still exhibit chronic fatigue syndrome (CFS). This makes the contention of a ‘pandemic’ of AFS unlikely.

Many complementary practitioners consider that daily life can ‘wear down’ one’s adrenals and that this leads to a depletion of adrenal hormone reserve and a life-affecting reduction in adrenal hormones, especially cortisol. It has been suggested that the hyperadrenia (over production or excretion of cortisol and other stress hormones) related to acute and chronic stress may eventually lead to hypoadrenia, matching the exhaustion / fatigue phase of the general adaptation syndrome. However, many people presenting purported symptoms of adrenal fatigue show normal cortisol levels and this contention lacks reliable verification in studies, and the diagnosis of adrenal fatigue is not one that is defined nor recognised.

The diagnosis of adrenal fatigue is often made primarily by an Adrenal Fatigue Questionnaire (example: http://www.adrenalfatigue.co.nz/dr-wilsons-adrenal-fatigue-questionnaire/).

This questionnaire has not been validated against any known markers of adrenal insufficiency. A common criticism of the questionnaire is that it is so broad as to encourage an Adrenal Fatigue diagnosis in most people. A veritable ‘catch-all’ of symptoms can be found in relation to AFS including psychological disorders, subjective symptoms (such as ‘brain-fog’), the use of coffee, tea and alcohol, physical signs such as dark-circles under the eyes, dry skin, and other medical conditions. The questionnaire lists over 90 signs, symptoms and comorbidities that could, in the opinion of AFS adherents, indicate the presence of AFS. This plethora of symptoms and co-morbidities makes a diagnosis of AFS likely, despite there being little evidence for it. More worryingly, a false diagnosis could be extremely dangerous in cases where there is an underlying and more serious condition. These could include a range of fatigue-inducing disease ranging from diabetes and metabolic disorder to cardiovascular disease, cancer and diagnosable (i.e. actual) adrenal insufficiency.

In a 2012 editorial in the Journal of Orthomolecular Medicine, Jonathon Prousky likens Adrenal fatigue, or Mild Adrenocortical Deficiency (MAD) to psychiatric disorders —i.e. they can be seen in symptoms and effects observed by treating those symptoms. However, a flaw in this argument is that there is a claimed pathological aetiology (reduced cortisol) in AFS, which cannot be reliably demonstrated in cohorts with supposed ‘Adrenal Fatigue’. Therefore, the basis for the diagnosis loses its veracity, and further, there is a grave risk of causing harm due to people not seeking an accurate diagnosis of other potential problems which may be causing the presenting symptoms. It is also contentious to justify a condition based upon treatments that are...
related to an improvement in symptoms when these have not been validated in controlled trials to adjust for the placebo effect. Notwithstanding that many clinical interventions are likely to promote an improvement in symptoms for many people, despite not having anything to do with a validation of a purported disease or disorder.

An exploration of the published literature is itself limited by the near dearth of research addressing ‘Adrenal Fatigue’ and its proper description, definition and diagnosis. Because of this lack of evidence there is no credible and validated basis for which to diagnose AFS and treat on this basis. Because of the paucity of literature concerning AFS, a broad search, inclusive of the term “adrenal fatigue” was conducted in Medline complete, CINAHL, Alt Health Watch, EBSCO Psychology and Behavioural Sciences Database and Sport Discus and in addition searched for tangential literature for chronic fatigue and related disorders in order to summarise the available information which may influence our position on the topic of AFS.

The common term for chronic states of fatigue is Chronic Fatigue Syndrome (CFS) and this is far better elucidated in the literature than the topic of AFS. In fact, almost the entirety of the available, published evidence is related to CFS and not AF. Chronic fatigue syndrome has no clear aetiology. Some neuroendocrine disturbances and reduced hypothalamic-pituitary-adrenal (HPA) axis function have been observed in people with CFS but it is unclear as to whether these dysfunctions are causative, resultant or corollary to the condition.

The HPA axis and fatigue

The HPA axis plays a major role in the regulation of responses to stress and CFS, fibromyalgia syndrome (FMS), chronic pelvic pain and post-traumatic stress disorder (and perhaps chronic back pain) are characterized by alterations in HPA axis activity. However, the role of the HPA axis alterations in these stress-related disorders is not clear. Most studies have shown that the HPA axis is underactive in the stress-related disorders, but contradictory results have also been reported, which may be due to the patients selected for studies, the methods used for the investigation of the HPA axis, the stage of the syndrome when the tests have been done and the interpretation of the results. While both CFS and FMS patients are shown to have central HPA dysfunction, the dysfunction in CFS is at the pituitary-hypothalamic level while the dysfunction in FMS is more related to dysfunction at the hypothalamic and supra-hypothalamic levels. However, even if the HPA axis dysfunctions are secondary to other factors, they are probably a relevant factor in symptom propagation in CFS. Hypothalamic-pituitary-adrenal axis dysfunction has been found in a high proportion of CFS patients and may include enhanced corticosteroid-induced negative feedback, basal hypocortisolism, attenuated diurnal variation, and a reduced responsivity to challenge. Given the inter-individual variation in the effectiveness of existing biological and psychological treatments, the need for novel treatment strategies such as those which target the HPA axis is clear. It has been hypothesised that HPA axis hypofunction in CFS reflects a fundamental, persistent dysregulation of the stress system. As a result, a disturbed balance between glucocorticoid and inflammatory...
signalling pathways may give rise to a pathological cytokine-induced sickness response that may be a common pathway underlying CFS symptoms, especially effort/stress intolerance and pain hypersensitivity. \(^\text{10}\) HPA axis changes seem clinically relevant, as they are associated with worse symptoms and/or disability and with poorer outcomes to standard treatments for CFS. Low activity levels, depression and early-life stress appear to reduce cortisol levels, whereas the use of psychotropic medication can increase cortisol. HPA-axis dysregulation and hypocortisolism are extremely important conditions that have not received appropriate attention until recently and hypocortisolism may be a fairly common phenomenon associated with stress. \(^\text{11}\) Of additional interest is the observation that psychological symptoms, particularly disturbances in mood and anxiety, are equally prominent in this condition. At this time, several reports have provided replicated evidence of disruptions in the integrity of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. It is notable that the pattern of the alteration in the stress response apparatus is not reminiscent of the well-understood hypercortisolism of melancholic depression but, rather, suggests a sustained inactivation of central nervous system components of this system. Recent work also implicates alterations in central serotoninergic tone in the overall pathophysiology of this finding. The implications of these observations are far from clear, but they highlight the fact that, though chronic fatigue syndrome overlaps with the well-described illness category of major depression, these are not identical clinical conditions. \(^\text{12}\)

**AFS, CFS and cortisol**

A key tenet of Adrenal Fatigue is that there is persistent suppression of cortisol production and / or release. Interestingly a significant correlation has been observed between a higher score on the Adrenal Fatigue Severity Questionnaire with *higher*, not lower, levels of cortisol and ACTH. Significant decreases in the levels of cortisol (\(p=0.001\)) and ACTH (\(p=0.001\)) were found in the participants with moderate to high physical activity compared to those with mild or sedentary activity. The decrement in adrenal hormonal levels positively correlated \((p=0.01, r=0.976)\) with improvements in the adrenal fatigue status and severity index, especially in the physically active participants. \(^\text{13}\) So higher stress was related to higher cortisol, which we would expect, and this was mitigated by exercise as were indicators of AFS. This is in contrast to what is commonly reported for AFS, i.e. that there is persistent hypoadrenia and that this is worsened by intense exercise.

Some studies have shown a degree of cortisol suppression in those with CFS. Cortisol levels have been demonstrated to be lower in adolescent CFS-patients than in healthy controls, with this mild hypocortisolism significantly correlated to the amount of sleep. Most studies though show little difference in baseline cortisol between those with and without CFS, change from baseline in response to stress is reduced in those with CFS\(^\text{15}\) and morning, waking CFS may be reduced, compared to healthy controls. \(^\text{16}\) It has also been demonstrated that in CFS urinary free cortisol and cortisone concentrations show normal diurnal rhythm, but levels were lower across the cycle in CFS. Urinary cortisol metabolites also show a normal diurnal rhythm, and levels of
these are not significantly different between CFS and controls at any time.\textsuperscript{17} This is in contrast to the often reported variations in daily cortisol response observed for those purported to be suffering from AFS (and for which there is no data that we are aware of from peer-reviewed research.) Little effect has been observed on daily cortisol levels as a result of stress tests in those with CFS.\textsuperscript{18} And there appears to be no significant difference was found between patients with CFS and controls for basal levels of morning cortisol and 24-h urinary free cortisol.\textsuperscript{19} Likewise total urinary cortisol and cortisol metabolites are not significantly different between CFS patients and controls.\textsuperscript{20} The findings of normal urinary cortisol metabolite excretion in patients with CFS is in variance with earlier reports that CFS is a hypocortisolaemic state. If serum and saliva cortisol levels are lower in CFS, this would suggest that metabolic clearance of cortisol is faster in patients with CFS than controls. These results in totality do not lend support to the theory that patients with chronic fatigue syndrome have a low adrenal reserve but there may be some minor variations in cortisol response and metabolism. However, it is unclear whether these responses are corollary, causative or resultant from the fatigue, and from other factors likely to be causing fatigue (such as the observed correlation between cortisol dysfunctions and sleep). Despite this there is some evidence that while pre-treatment salivary cortisol levels do not predict treatment outcomes, normalization of cortisol is associated with treatment success.\textsuperscript{21} Patients with chronic fatigue syndrome have also demonstrated enhanced suppression of salivary free cortisol after the administration of 0.5 mg of dexamethasone in comparison to the control subjects.\textsuperscript{22} 

\section*{CFS and other hormones}

The effects on the HPA axis in CFS are inconsistent. It has been suggested that many other factors may be contributing to HPA axis alterations in chronic fatigue syndrome, including sleep disturbance, inactivity, altered circadian rhythmicity, illness chronicity, concomitant medication and comorbid psychiatric disturbance. These sources of heterogeneity need to be considered in future studies, and may explain the inconsistent findings to date.\textsuperscript{23} Patients with CFS have demonstrated subtle alterations in HPA axis activity characterized by reduced ACTH over a full circadian cycle and reduced levels during the usual morning physiological peak ACTH secretion.\textsuperscript{24} Reduced ACTH levels have been observed in CFS patients during the 8 am to 10 am period as well, however, no significant abnormalities in the levels of cortisol, GH, and PRL in patients with CFS were observed over the full cycle compared with control subjects.\textsuperscript{25} In other studies there has been observed elevated evening ACTH and reduced evening cortisol.\textsuperscript{26} And yet others, in response to various biochemical stressors; human corticotropin-releasing hormone (CRH), insulin stress test, and D-fenfluramine (a stimulant anorectic) baseline cortisol concentrations were significantly raised in the chronic fatigue syndrome group for the CRH test only. Baseline ACTH concentrations did not differ between groups for any test. ACTH responses to human CRH, the insulin stress test, and D-fenfluramine were similar for patient and control groups. Cortisol responses to the insulin stress test did not differ between groups, but there was a trend for cortisol responses both to human CRH and D-fenfluramine to be lower in the chronic fatigue syndrome group.\textsuperscript{27}
release of ACTH (but not cortisol) in response to opiate drugs may also be blunted in CFS subjects compared with controls.\textsuperscript{28} Release of ACTH (but not cortisol) in response to ipsapirone challenge was significantly blunted in patients with CFS.\textsuperscript{29} Significantly lower ACTH response levels have been observed in response to a psychosocial stress test and exercise test, with no differences in plasma total cortisol responses. Also, salivary-free cortisol responses did not differ between groups in the psychosocial stress test and the exercise suggesting that CFS patients are capable of mounting a sufficient cortisol response under different types of stress but that on a central level subtle dysregulations of the HPA axis exist.\textsuperscript{30} Morphological changes have also been noted in some with CFS. Right and left adrenal gland bodies were reduced by over 50\% in CFS subjects in one study.\textsuperscript{31} DHEA and DHEAS are significantly lower in the CFS compared to healthy controls.\textsuperscript{32} When CFS has been compared to diagnosed adrenal insufficiency (AI) and a control group (C) without CFS or AI it has been found that in some subjects cortisol response is preserved, while in others it is similar to one found in secondary adrenal insufficiency.\textsuperscript{33} CFS patients do not show an exaggerated secretion of LPS-induced cytokines. Although cortisol responses to stress were normal, pro-inflammatory cytokine levels in CFS patients were significantly attenuated. Possible intracellular mechanisms, such as for example an enhanced sensitivity to inhibitory effects of glucocorticoids, a diminished responsivity to catecholaminergic stimulation, and a disruption of intracellular activation are discussed. Basal levels of stimulated pro-inflammatory IL-6 levels are generally related to fatigue scores. However, in CFS patients this association is of greater magnitude and can also be observed for TNF-alpha.\textsuperscript{34}

**Conclusion**

There are significant variations in individual characteristics of chronic fatigue. It is likely that there is some dysfunction of the HPA axis present, especially with respect to ACTH and possibly DHEA. Baseline and total cortisol levels do not appear to be significantly different between those with CFS and controls but there may be subtle and individual-dependent differences in cortisol response, and metabolism and clearance. However, the causative, corollary or resultant nature of these and other findings are yet to be properly elucidated.

There is an almost complete lack of research on the condition characterised as ‘Adrenal Fatigue Syndrome’ and until there can be proper validation testing of questionnaires, and a definitive and validated diagnostic protocol for the condition, this diagnosis should not be used. We further caution that diagnosis by alternative practitioners who are not qualified and registered should be avoided and that misleading diagnoses may put patients at risk due to the non-detection of other conditions.

We believe that there are ‘return to play / return to life’ strategies that are evidence-based, for our clients presenting with fatigue, that do not rely on the diagnosis of a ‘pseudocondition’ that is yet to be described properly and using these strategies offers better potential for positive treatment outcomes.
References

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