REVIEW

Diagnosis and Treatment of Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysfunction in Patients with Chronic Fatigue Syndrome (CFS) and Fibromyalgia (FM)

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Abstract

There is controversy regarding the incidence and significance of hypothalamic-pituitary-adrenal (HPA) axis dysfunction in chronic fatigue syndrome (CFS) and fibromyalgia (FM). Studies that utilize central acting stimulation tests, including corticotropin-releasing hormone (CRH), insulin stress testing (IST), d-fenfluramine, ipsapirone, interleukin-6 (IL-6) and metyrapone testing, have demonstrated that HPA axis dysfunction of central origin is present in a majority of these patients. However, ACTH stimulation tests and baseline cortisol testing lack the sensitivity to detect this central dysfunction and have resulted in controversy and confusion regarding the incidence of HPA axis dysfunction in these conditions and the appropriateness of treatment. While both CFS and FM patients are shown to have central HPA dysfunction, the dysfunction in CFS is at the pituitary-hypothalamic level while the dysfunction in FM is more related to dysfunction at the hypothalamic and supra-hypothalamic levels. Because treatment with low physiologic doses of cortisol (<15 mg) has been shown to be safe and effective and routine dynamic ACTH testing does not have adequate diagnostic sensitivity, it is reasonable to give a therapeutic trial of physiologic doses of cortisol to the majority of patients with CFS and FM, especially to those who have symptoms that are consistent with adrenal dysfunction, have low blood pressure or have baseline cortisol levels in the low or low-normal range.

Key words: HPA axis dysfunction; hypothalamic-pituitary-adrenal axis; chronic fatigue syndrome; fibromyalgia; CFIDS; cortisol, hydrocortisone

Introduction

Chronic Fatigue Syndrome (CFS) and fibromyalgia (FM) are disabling conditions that are shown to be present in 0.5-5% of the population and often coexist (1-3). Treating CFS and FM patients is often frustrating for physicians as there is no clear etiology or treatment, and the use of standard recommended treatments that don't address the underlying pathophysiology, including NSAIDS, antidepressants and muscle relaxants, are largely ineffective and have significant side-effects (4-7). Reliance on these medications results in a poor prognosis and is unsatisfying for both patients and physicians (8-18). There is unlikely a single causative agent or process occurring in these conditions. The hypothalamic-pituitary dysfunction that is present in the majority of CFS and FM patients results in HPA axis dysfunction that is often not detected by standard testing done in a clinical setting, as these tests are designed to detect primary adrenal insufficiency and have poor sensitivity for secondary or tertiary adrenal insufficiency (19-58). In addition, this hypothalamic-pituitary dysfunction results in secondary and/or tertiary hypothyroidism (as well as evidence of thyroid resistance) that is not detected with standard thyroid testing (27,59-69), and low growth hormone production that is also not detected by standard testing (27,60,70-74). There has also been shown to be associated mitochondrial dysfunction (75-78), sleep disorder (79-84), immune dysfunction (85-95), chronic infections (96-105), autonomic dysfunction (106-108), gastrointestinal dysfunction (109-113) and coagulation dysfunction (114-119) in these patients.

A multi-faceted treatment approach that addresses the above abnormalities, including treatment with hormonal supplementation despite seemingly normal levels and treatment of the mitochondrial dysfunction, sleep disorder, chronic in-

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fections, immune dysfunction, gastrointestinal dysfunction and the coagulation dysfunction is now the standard of care by experts who specialize in the treatment of CFS and FM (65,69,78,120-146). There are seemingly contradictory studies regarding the incidence of HPA axis dysfunction in these conditions. However, a clearer understanding of pathophysiology of these conditions demonstrates that the negative results are largely due to a lack of sensitivity of the testing utilized and the improper use of standard cutoffs to denote normal function and not because there is an absence of HPA axis dysfunction.

Evidence for Significant HPA Axis Dysfunction

There are a large number of studies that assess basal cortisol levels in CFS and FM patients as a primary focus or as part of a subsequent stimulation test. These are of limited value as they fail to assess the function of the HPA axis during stress and lack sensitivity in detecting central HPA axis dysfunction. The majority of studies measuring 24-hour urine cortisol levels in CFS and FM patients have demonstrated significantly lower values in the CFS/FM patients (22,29,30,32,33,45-49). As with baseline measures of serum cortisol, twenty-four hour urine cortisol lacks sensitivity at detecting central HPA axis dysfunction because it does not necessarily assess the HPA axis dysfunction during stress. Additionally, the wide individual variation of 24-hour cortisol excretion in normal individuals due to varying stress levels over the 24 hours significantly decreases sensitivity. Ten studies were identified that assess 24-hour urine cortisol levels in CFS and FM patients with six demonstrating a significant decrease in 24-hour urine cortisol in CFS/FM patients and one demonstrating reduced levels that did not reach statistical significance (22,29,30,32,33,45-49). The majority of studies that measured 24-hour urine involve very small numbers of patients and controls, limiting the sensitivity, while the largest study to date by Cleare et al involving 121 CFS patients and 64 controls demonstrated significantly decreased 24-hour urine cortisol levels in CFS patients that averaged approximately 30% lower than healthy controls (47).

The lack of sensitivity of the 24-hour urinary cortisol levels is demonstrated by the fact that two of the four negative studies also performed stimulation tests (IST or IL-6) and both demonstrated HPA axis dysfunction despite having normal or non-significantly reduced 24-hour urine cortisol levels (32,33).

One of the two remaining negative studies was a small study by Maes et al in which 24-hour cortisol levels were measured in patients with FM, major depression and post traumatic stress disorder (PTSD) compared to normals (49). This study consisted of 14 FM patients and 17 normals.

The contradictory findings of this study may be explained by the fact that it appears that they excluded patients who were on any medications and it also appears that these patients were not previously diagnosed with FM prior to the study. This would tend to include only those with very mild disease and exclude those with moderate or severe symptoms, who would more likely have been previously diagnosed with FM and require medications for symptomatic relief.

The second of the two remaining negative studies was by Young et al that compared 24-hour urinary cortisol between 22 CFS patients and 24 controls (48). The difference in these results may be explained by different patient characteristics than the other studies, including the fact that these patients had the shortest mean duration of symptoms of all the 24-hour urine cortisol studies, being only 2.5 years, compared to the other studies that had mean durations of 3.6 to 9.7 years.

There are a large number of seemingly contradictory studies that measure basal cortisol levels or utilize standard dynamic ACTH stimulation tests to evaluate HPA axis function in CFS and FM, which has led to confusion and controversy as to the incidence of HPA axis dysfunction in these conditions. One likely contributing cause of the confusion and controversy is that it has been shown that the plasma cortisol immunoassays used by the majority of laboratories, institutions and studies suffer from considerable inaccuracy and variance and can significantly overestimate serum cortisol levels when compared to gold standard assays such as gas-chromatograph/mass spectrometry (GC/MS) and high performance liquid chromatography (HPLC). This has led to controversy, a high degree of misdiagnosis and the misclassification of patients as having normal HPA function despite significant dysfunction or severely underestimating the severity of the dysfunction (147-151).

For instance, Cohen et al compared three commonly used cortisol immunoassays (Bayer Advia Centaur, Abbott TDx and DPC Immulite 2000) and HPLC to determine serum cortisol levels and found a huge variation in results with concordance in only 44% of patients. The immunoassays were shown to overestimate the serum cortisol levels by an average of 70% (35%, 79% and 95%, respectively, for each assay) without appropriate adjustment of the reference ranges by the assay manufacturers. This resulted in the misclassification of 44-56% of patients depending on the assay used. The Centaur assay produced results that were over 480% of that of the HPLC standard, the TDx assay produced results that were up to 590% of the standard and the Immulite assay produced results that were 770% of the standard (147).

De Brabandere et al evaluated the performance of three cortisol immunoassays commonly used by laboratories in the U.S. and Europe (Diagnostic Products Corp (DPC), Amerlex and Baxter Diagnostics)(149). They measured cor-

tisol levels in 15 patient samples and 10 commercially prepared control serum standards in duplicate and compared the results with those obtained via the gold-standard GC/MS. The measured cortisol results on the commercially prepared control samples showed that the assays averaged only 11% higher than when measured via the GC/MS. However, the results on the patient samples demonstrated a severe inaccuracy of these assays commonly used in commercial laboratories. The mean deviation of the reported cortisol concentrations that were below 13 ng/ml (370 nmol/l) was +21%, +91% and +83% for each assays, respectively. These differences were not reflected in the respective kit reference ranges. For instance, the upper reference range for the Amerlex assay is only 12% higher than the upper reference range of the DPC assay despite averaging over 40% higher on the same specimens. Baxter quotes an upper reference range that is significantly lower than the Baxter assay (552 nmol/l vs. 690 nmol/l) despite having the strongest positive overall bias. The lower limit for the Amerlex assay is only 9% greater than the DPC assay (152 nmol/l vs. 158 nmol/l) despite averaging over 60% higher on the same specimens. These studies demonstrate that a seemingly normal baseline or stimulated cortisol level reported by a laboratory cannot be relied upon to accurately rule out significant hypocortisolism.

Further confounding results is the fact that CFS and FM patients are a very heterogeneous group in terms of illness severity and duration and associated psychiatric comorbidities, which likely influence HPA dysfunction. In addition, there is the significant normal variation in cortisol levels in normal individuals. A more important fact is, however, that a multitude of studies have demonstrated the HPA axis dysfunction in these conditions is central (hypothalamic or pituitary), not a primary adrenal insufficiency. Consequently, it is of no surprise that these studies appear to have inconsistent results because baseline cortisol levels and ACTH dynamic testing have very low sensitivities in detecting central HPA axis dysfunction and fail to diagnose the majority of patients with known significant central HPA axis dysfunction (29,31,35-44). Because a normal result with such testing does not rule out significant dysfunction, it is not a recommended means of detecting this abnormality. Low dose (1 ug ACTH) stimulation may be slightly more sensitive than conventional (250 ug ACTH) testing, but it still suffers from very poor sensitivity and misses approximately 50% of individuals with established central hypoadrenalism determined by IST, d-fenfluramine, ipsapirone, CRH stimulation or metyrapone testing (35-41,44,152).

Studies that use appropriate testing for individuals with secondary or tertiary hypoadrenalism, including IST, metyrapone testing and stimulation testing using CRH, IL-6 and d-fenfluramine, have consistently demonstrated significant HPA axis dysfunction in CFS and FM patients. Of the 16 studies identified that used such testing, all but one of these studies demonstrated HPA axis dysfunction with abnormal ACTH and/or cortisol secretion (19-33,41).

Chronic Fatigue Syndrome

Demitrack et al studied the functional integrity of the various components of the HPA axis in 30 patients with CFS and 72 normals with an average duration of illness of 7.2 +/- 1.0 years. They performed CRH (bovine 1ug/kg) stimulation testing and graded ACTH stimulation testing. They also compared the levels of evening serum free and total cortisol, cortisol binding globulin (CBG) and corticotropin releasing hormone (CRH) in the cerebrospinal fluid and measured 24-hour urinary cortisol levels (19).

They found significantly lower evening cortisol levels in CFS patients vs. controls (3.2 ug/ml +/- 0.3 vs. 5.3 +/- 0.73) and 24-hour urinary free cortisol excretions that were 40% lower in the CFS patients (122.7 nmol/L vs. 203 nmol/L). Interestingly, the level of cortisol binding globulin CBG was also significantly higher in the CFS patients making the free cortisol index almost 70% lower in these patients (2.9 vs. 8.9). This elevated CBG is significant because it results in an overestimation of bioavailable and free cortisol levels, and if confirmed, it may be further contributing to the lack of sensitivity of both basal and dynamic testing by overestimating cortisol levels in these patients because most of the studies have utilized total cortisol levels when comparing CFS and FM patients to normals. This potential of overestimation of serum cortisol levels would be additive to the overestimation of actual cortisol levels by commonly used immunoassays discussed earlier (147,149).

This study found a significant attenuated net integrated ACTH response to CRH (128 +/- 26.4 vs. 225 +/- 34.5)(P < 0.04) demonstrating central HPA axis dysfunction. With ACTH stimulation testing, there was an initial increased sensitivity to ACTH with a subsequent reduced maximal response. Although this cortisol response to ACTH was clearly abnormal for all of the patients with CFS in this study, the dose response curve varied. There was an initial exaggerated response followed by an abnormally blunted response, which is not the case for patients with simple primary or secondary adrenocortical insufficiency and demonstrates hypothalamic involvement in the HPA axis dysfunction in these patients (19).

Scott et al 1998 performed CRH (bovine 100 ug) stimulation tests on 14 CFS patients with an average illness duration of 4.8 +/-0.6 years (range 1.5-10 years) as compared to 14 controls. There were lower basal ACTH and cortisol levels in the CFS patients, but it did not reach statistical significance. The delta-ACTH response in the CFS group (21.4 +/- 4.3 ng/l) was significantly lower than that in the controls

(51.9 +/- 8.5)(p < 0.005). The delta-cortisol levels were also similarly attenuated in the CFS group (197.7 +/- 21.6 nmol/l) vs. the healthy controls (310.5 +/ 21.6 nmol/l), demonstrating central HPA axis dysfunction in these patients (20).

Scott et al 1999 again evaluated the HPA axis in CFS patients by performing CRH (bovine 100 ug) stimulation tests on 13 CFS patients as compared to 13 controls. Patients had a mean duration of illness of 5.0 years. This study found that 8 out of 13 CFS patients had lower stimulated ACTH levels than the lowest ACTH response in the normal controls, being 21.0 +/- 4.5 ng/l in the CFS patients as compared to 57.8 +/- 11 ng/l (p = .005) in normal controls. The delta-cortisol response in 9 of the 12 CFS patients was lower than the lowest delta-cortisol in the control group (157.6 +/- 40.7 nmol/l in the CFS group compared to 303.5 +/- 20.9 nmol/l in the control group (p = 0.01)), again demonstrating central HPA axis dysfunction in CFS patients (21).

Cleare et al 2001 performed CRH (human 1 ug/kg), IST and d-fenfluramine stimulation testing in 37 medication free CFS patients. Patients had a mean duration of illness of only three years. Thirty-two patients were treated with low dose (either 5 mg or 10mg cortisol per day). With human CRH stimulation testing, there were similar ACTH responses between groups with AUC cortisol values being reduced in CFS patients as compared to controls (206 +/-213 nmol/l-h vs. 313 +/-257 nmol/l-h (p = 0.069)). When ACTH was controlled for, the CFS patients had a significantly reduced release of cortisol (p = 0.016). The difference in the abnormality seen in this study as compared to Demitrack et al, Scott et al 1998 and Scott et al 1999 could be due to different patient characteristics. The average duration of illness in this study was only three years, while the average duration of illness in the Demitrack et al and the Scott et al studies were 7.2, 5 and 4.8 years, respectively. In addition, human CRH was used at 1 ug/kg as compared to bovine CRH, which is more potent and has a longer half life, being used in the Demetrik and Scott et al studies. Scott et al used human CRH at a higher average dose of 100 ug, as well. Interestingly, the patients who responded to treatment with clinical improvement had a normalization of the previously blunted cortisol response to CRH, while those who did not clinically respond had no significant change in the endocrine parameters before and after treatment, demonstrating a lack of adrenal suppression and a potential improvement in HPA axis function with physiologic doses of cortisol (22).

With d-fenfluramine stimulation testing, there was again a trend for lower cortisol response (p = 0.077) without a significant difference in ACTH levels. When ACTH responses were controlled for, cortisol responses were significantly reduced (p =0.033). There was no significant difference in ACTH or cortisol responses between groups with IST assessment, but there was significantly reduced urine 24-hour cortisol levels in CFS patients vs. controls (p = 0.025) (22).

Inder et al compared 24-hour urinary cortisol levels and performed CRH (bovine 1ug/kg) stimulation testing on 12 CFS patients and 11 controls. They found no significant difference in 24 hour urinary cortisol levels, basal ACTH, basal cortisol levels, stimulated ACTH or stimulated cortisol levels. The illness duration was not stated. This difference may be explained by the heterogeneity of this population and the small study size. The study size would require a 40% difference between groups to distinguish a difference (23).

Gaab et al performed IST on 18 CFS patients with an average illness duration of 5.6 years (range 1.4- 14 years) and 17 controls. They found a significantly blunted ACTH response to IST that was 40% less in the CFS group compared to controls, demonstrating central HPA axis dysfunction in these patients. Interestingly, they also performed two procedures mimicking real-life stressors and also found significantly lower ACTH responses in the CFS patients as compared to controls, demonstrating central HPA axis dysfunction (24).

Bearn et al performed IST and d-fenfluramine stimulation testing on nine CFS patients and ten normal controls. The average duration of illness was 5.7 years with a range of 1-15 years. All but one had significant myalgia and were not on medication for 12 weeks prior to study. There was a delayed and attenuated ACTH and cortisol response to IST that was consistent with hypothalamic-pituitary dysfunction but due to the small sample size, it did not reach statistical significance (25).

There was a significantly increased ACTH response with d-fenfluramine stimulation with a decreased cortisol response that also did not reach statistical significance due to the sample size. This is consistent with hypothalamic dominant dysfunction with a centrally inhibited adrenal response to ACTH. A hypothalamic dysfunction with a primary adrenal dysfunction is also possible, but unlikely, considering normal adrenal response to ACTH under different study conditions. These patients' ACTH and cortisol response was more indicative of FM patients (discussed below) and demonstrates a more hypothalamic/supra-hypothalamic dominant dysfunction that is seen in the FM patients as compared to the hypothalamic/pituitary dysfunction typically seen in CFS patients. The authors did not state if any of the patients also met the criteria for FM, but all but one had significant myalgia, so it is likely that they did have FM, thus explaining the results (25).

Dinan et al 1997 demonstrated a blunted release of ACTH in response to ipsapirone, a serotonin agonist, in 14 CFS patients vs. 14 controls (4.4 +/- 0.6 ng/l vs 14.6 +/- 1.6 ng/l), demonstrating central HPA axis dysfunction in these patients (26).

Fibromyalgia

Riedel et al 1998 injected CRH (bovine 100 ug) along with a simultaneous injection of TRH, GHRH and LHRH in 16 FM patients and 17 controls. They found elevated basal levels of ACTH and cortisol and an exaggerated ACTH response with no difference in stimulated cortisol levels, demonstrating a hyporesponsive adrenal response to ACTH. This is most consistent with a hypothalamic or a supra-hypothalamic dominant dysfunction rather than a primary adrenal insufficiency. They also found significantly elevated prolactin levels on stimulation with significantly reduced TSH secretion, free T3 production and growth hormone secretion, all demonstrating hypothalamic-pituitary dysfunction (27).

Griep et al 1993 performed CRH (human 100 ug) stimulation testing and IST on 10 FM patients and 10 controls. They also found a statistically significant enhanced ACTH response and a relative adrenal hypo-responsiveness in the FM patients as compared to controls with both the IST and CRH testing, indicating a tertiary (hypothalamic or supra-hypothalamic level) hypoadrenalism (28).

Griep et al 1998 compared the HPA axis function in 40 FM patients with an average illness duration of 10.7 +/- 7.2 years, 28 patients with chronic low back pain and 14 controls. They used a combination of tests that included CRH (human 100ug) stimulation testing, very low dose (0.025 ug/kg) and low dose (0.1 ug/kg) ACTH stimulation tests and 24-hour urinary cortisol evaluations. This study also showed a significantly abnormal HPA axis in FM patients after CRH stimulation with an ACTH hyper-responsiveness and a relative adrenal hypo-responsiveness, indicating a tertiary (hypothalamic or supra-hypothalamic level) hypoadrenalism (29).

There was also significantly decreased 24-hour urine cortisol levels in the FM patients compared to the controls, but there was no difference in the evoked cortisol levels with either the very low dose or the low dose ACTH simulation tests between the three groups, indicating that there is not a primary adrenal dysfunction. This study also further demonstrates and supports other studies that show that ACTH stimulation testing is an insensitive means of detecting central HPA axis dysfunction and is, therefore, not a recommended method of evaluation in these patients (29,31,36-39,152). Crofford et al performed CRH (bovine 1 ug/kg) testing and 24-hour urinary free cortisol levels in 12 FM patients and 12 controls. The FM patients had an average duration of illness of 6.2 +/- 3.1 years. This study found a non-statistically significant exaggerated ACTH response to CRH with a statistically significant decrease in net cortisol response (p < 0.02), demonstrating a hypothalamic dominant dysfunction of the HPA axis of FM patients. They also found a statistically significant decrease in 24-hour urinary free cortisol levels (p < 0.002) (30).

Calis et al performed metyrapone testing and 1 ug ACTH stimulation tests on 22 FM patients and 15 matched controls. After metyrapone administration, 95% of FM patients had lower 11-deoxy-cortisol than the lowest level in the healthy controls, while only 45% of FM patients had low cortisol responses to the ACTH simulation test (31). This demonstrates central HPA axis dysfunction in these patients, but ACTH stimulation testing will miss approximately half the individuals with significant dysfunction and is not a recommended means of evaluating the HPA axis in these patients (29,31,36-39,152).

Kirnap et al performed IST as well as 1 ug and standard ACTH stimulation testing on 16 FM patients and 16 controls. They found significant reduced basal cortisol levels in the FM group (p < 0.0001) as well as significantly reduced responses to all three stimulation tests (p < 0.0001), demonstrating significant central HPA axis dysfunction in these patients (ACTH levels were not measured). They also found that if the standard cutoffs were used with the ACTH simulation test, most of the patients would have been misdiagnosed as normal (40).

Adler et al performed stepped hypoglycemic hyperinsulinemic clamp studies, performed ACTH infusions and evaluated 24-hour urinary free cortisol levels in 15 FM patients and 13 controls. The average duration of illness was 9 +/- 8 years. Baseline 24-hour urinary free cortisol levels were not significantly different between the two groups, but basal ACTH levels were significantly lower in FM patients (2.8 +/- 1.7 pmol/l) as compared to the control group (5.0 +/- 2.9 pmol/L). The ACTH levels in response to hypoglycemia were significantly reduced in the FM group, with an average integrated response being 68% of that of the control group. Baseline hypoglycemic stimulated and ACTH stimulated cortisol levels were not significantly different. These results of a diminished ACTH response are in contrast to the above studies demonstrating an exaggerated ACTH response in FM patients and more similar to the results involving CFS patients. There is significant overlap in those diagnosed with FM and CFS and this may have been a factor in this study. Additionally, this group had a much longer duration of illness than the FM patients in the previously discussed studies and different methodologies could also explain the differences (33).

Torpy et al performed 24-hour urine cortisol levels and administered IL-6 stimulation tests to 13 FM patients and 8 controls. There was a trend to lower 24-hour urine cortisol levels in FM patients vs. controls (40.7 +/- 5 ng/24-hours vs. 57.0 +/- 9.9 ng/24-hours) although it did not reach statistical significance. They found no significant difference in peak cortisol or ACTH levels between the two groups, but the FM group was shown to have a significant delay in the ACTH response, with peak levels not occurring until 96 +/- 6 minutes

vs. 68.6 +/- 10.3 minutes in the control group. This delayed ACTH response with a trend to lowered 24-hour urine cortisol levels supports a dysfunction at or above the hypothalamic level. This delayed ACTH response as compared to the exaggerated ACTH response to CRH in FM probably reflects differences in the principle site of action of these agents and supports HPA axis dysfunction at or above the hypothalamic level (32).

Treatment

In a randomized crossover trial, Cleare et al 1999 treated 32 CFS patients with a mean duration of illness of 3 years (range 2.3-3.75 years) with low dose cortisol (5-10 mg/day) and placebo for one month in a randomly assigned order. This study found significant improvements in fatigue and disability in those treated with low dose cortisol but not with placebo (p = 0.009). Twenty-eight percent of the patients improved to normal levels with treatment, and follow-up IST demonstrated that there was no suppression of endogenous adrenal function with treatment. In fact, those who responded to treatment had an improvement in HPA axis function via CRH stimulation testing, demonstrating the effectiveness and appropriateness of this treatment (22,146).

Blockmans et al performed a 6-month randomized, placebo-controlled, double-blind, crossover study of 80 patients with CFS using a combination of 5 mg cortisol and 50 mcg of fludrocortisone. Patients had an average duration of illness of only 2.5 years (1.3-5). There was significant improvement in fatigue scores with treatment as measured with an Abbreviated Fatigue Questionnaire (p = 0.004), but there was a significant placebo response so it was not significantly different from placebo. There was no difference in fatigue scores as measured by a visual analog scale. There was significant improvement in the Mental Factor of the Short Form Health Survey compared to placebo and also in the Physical Factor but not compared to placebo. Depression scores improved with treatment vs. placebo. ACTH simulation tests were performed at 0, 3 and 6 months. The baseline ACTH stimulation tests were normal and none of the patients had any evidence of adrenal suppression with treatment (153).

The less impressive response in this study as compared to the Cleare study is potentially explained by different patient characteristics. These patients had a much shorter duration of illness and were recruited from different patient populations. The Cleare study recruited patients from clinics that specialize in CFS in England and Blockmans et al recruited patients from a tertiary care university hospital in Belgium, and they appeared to have excluded those with ulcers, hypertension, glaucoma or diabetes but did not exclude those with fatigue related illnesses. These patients appeared likely to be an especially heterogeneous group with a multi-

tude of disease processes.

Mckenzie et al performed a randomized, placebo-controlled, double-blind 12-week therapeutic trial with 25-35 mg of cortisol to 30 CFS patients and 35 controls. Patients met the more rigorous 1988 criteria for CFS and were assessed with a daily wellness scale for 12 weeks. The study found that 66.7% of patients improved with treatment, with most patients reporting a modest but significant difference vs. placebo as measured by at least a 5, 10 or 15 point improvement. A five or more point improvement was seen in 53% of the cortisol treated patients vs. 29% receiving placebo (p = .04), a 10 point improvement was seen in 33% of the cortisol treated patients vs. 14% of controls (p = .07) and a 15 point improvement was seen in 20% of cortisol treated patients vs. 6% of controls (p = .08)(154).

Three patients in the treatment group withdrew due to ineffectiveness and four withdrew from the placebo treatment (three due to ineffectiveness and one due to a rash). Five of the cortisol treated patients did not have pretreatment wellness scores so they could not be evaluated. There was no significant correlation between response and the pretreatment basal or ACTH stimulated cortisol levels. Five patients in the treatment group had a depressed cortisol response in the post treatment ACTH simulation testing. However, the doses used in this study are considered by many researchers and clinicians that specialize in CFS/FM to be inappropriately high for treatment of this condition (54,120,124,125,136,155-162) and significantly higher than the studies that demonstrate a lack of adrenal suppression with lower doses of 5-15 mg/day (22,120,146,153,156,162).

Teitelbaum et al performed a randomized, double-blind, placebo controlled, intent to treat study on 72 FM (69 also met CFS criteria) patients (38 active and 34 placebo) that documents the effectiveness of an integrative treatment approach to CFS and FM that includes low dose cortisol (7.5-20 mg/day) (120). The patients underwent an integrative multi-system treatment protocol based on an algorithm that took into account laboratory tests as well as signs and symptoms. Potential treatments included antidepressants, levothyroxin, cortisol, fludrocortisone, DHEA, testosterone and antimicrobial treatments. Cortisol was administered if there was a baseline cortisol level ≤ 12; the ACTH stimulated cortisol increase was < 7 at 30 minutes, < 11 at 60 minutes or the 60 minute cortisol was < 28; the HgbA1C was < 5.1; or if patients had three significant symptoms consistent with adrenal dysfunction. Cortisol was given to 29 of the 38 patients at some time during the 3 month study. Overall, patients had significant improvements vs. placebo in visual analog scores (p < 0.0002), the Fibromyalgia Impact Questionnaire (p <0.0005), the tender point index (p < 0.0001) and overall response (p < 0.0001). No patients were found to have any adrenal suppression with post-treatment ACTH simulation

tests. While this study does not separate out cortisol's overall effect, it provides the basis for demonstrating that an integrative multi-system treatment approach that includes low dose cortisol is highly safe, effective and appropriate in the treatment of these conditions. This integrative approach is now considered by many who specialize in the treatment of CFS/FM to be the current basic standard of care (65,69,120-146) and has served as a building block for more advanced therapies and algorithms. Interestingly, a sub-analysis demonstrated that antidepressants had no significant beneficial effect on the patients' outcome scores (p <.0001) (120).

Currently, our center has tracked over 500 consecutive patients that met the CDC criteria for CFS and/or the American College of Rheumatology criteria for FM (240 met criteria for CFS, 14 met the criteria for FM and 259 met criteria for both). The computerized tracking system consists of the tracking of the patients' average overall energy level and sense of well-being (SOWB) on each visit as well as the frequency and severity of 10 symptoms that includes fatigue, muscle pain, stiffness, cognitive function, headaches, insomnia, unrestful sleep, gastrointestinal dysfunction and sore throat. Before each visit, patients rated their energy and sense of well being on a scale of 1-10 (1 being low and 10 being high) and their individual symptom frequency and severity on a scale of 1-10 (10 being constant and 1 being rare for frequency and 10 being severe and 1 being mild for severity). Patients had seen on average 7.2 different physicians for treatment of their CFS and/or FM without significant improvement prior to being seen at our center. Patients were treated based on a multi-system integrative treatment algorithm that incorporates therapies based on the most recent understanding of the pathophysiology of these conditions (due to its complexity, a description of the algorithm is beyond the scope of this review). The treatment algorithm did include low dose cortisol after the second visit if symptoms were consistent with adrenal dysfunction based on 24 symptoms and/or having low blood pressure and/or having a baseline cortisol level in the low or low-normal range. If patients met the protocol criteria, they were given a therapeutic trial of 5-15 mg of timed-released cortisol per day. Patients were also given fludrocortisone if they had signs of neurally mediated hypotension.

Analysis revealed (prepublication ongoing data collection) that 94% of patients had overall improvement by the 4th visit with 75% noting significant overall improvement and 62% reporting substantial overall improvement. The majority of patients continued to improve in subsequent visits. The average energy levels and average SOWB increased significantly. The average energy level more than doubled by the 4th visit, going from an average of 2.98 at baseline to 6.39 at the 4th visit and then to 6.77 and 7.67 at the 7th and 9th visits, respectively. The average SOWB also more than doubled

by the fourth visit, increasing from a baseline average of 3.03 then increasing to 6.29, 7.45 and 6.83 on the 4th, 7th and 9th visit, respectively. There were no significant side-effects from low dose cortisol in these closely monitored patients (136).

Subsequently, over 40 physicians were trained to utilize a more simplified treatment algorithm in 17 centers across the country. In this multi-center study, over 4000 consecutive patients diagnosed with CFS and/or FM were treated with this simplified algorithm and tracked via the same computerized patient assessment system. This prepublication ongoing data collection demonstrated that 85% of patients improved by the 4th visit, with 56% and 40% reporting significant and substantial improvement, respectively, by the 4th visit. This increased to 62% and 46% by the 7th visit (137).

While these two studies are not placebo controlled and do not allow the evaluation of cortisol as a sole treatment of CFS/FM, as cortisol was only a part of the multi-system treatment protocol that included numerous therapeutic interventions, cortisol supplementation was shown to be a beneficial and safe therapeutic intervention with little or no risk as part of a multi-system integrative treatment protocol. It is extremely unlikely that such dramatic improvements were due to a placebo effect because these patients had been typically seen by numerous physicians without improvement and such patients have been shown to have little placebo responses (163).

Side Effects and Safety

Because physiologic doses of cortisol (<15 mg) do not increase levels beyond normal levels, it is exceedingly safe and is not associated with adverse effects associated with pharmacological doses of corticosteroids, including adrenal suppression, bone loss and immune suppression (22,54,120,136,137,146,153,155-157,162,164-176). A review by Jefferies of 1000 patient-years of treatment with physiological doses of cortisol found that the only undesirable side effect was acid indigestion and skin rashes due to allergies to the tablets' fillers in a few patients (155).

As opposed to pharmacological doses of corticosteroids, physiological doses (<15 mg) of cortisol have been shown not to cause adrenal suppression (22,120,146,153,156,162) and have been shown to actually improve HPA axis function (22). This is counterintuitive to what physicians are taught and have found with higher pharmacological doses of glucocorticoids. Also, physiologic doses of cortisol have been shown to improve cellular and hormonal immunity, including natural killer cell activity (155,157,164-171,177), which has been found to be a consistent abnormality in CFS patients (85-88). This is also counter-intuitive to physicians because of the well-known immune suppression that is seen with pharmacological doses of corticosteroids.

The longest randomized placebo controlled studies (over 2 years) that assessed bone loss with the use of low dose corticosteroids (≤ equivalent to 40 mg of cortisol) have demonstrated that there is no significant increase in bone loss vs. placebo with such treatment (172-176). The fact that these studies, while considered low dose, were considerably higher than the recommend doses for CFS and FM patients, demonstrates that using cortisol supplementation at doses less than 15 mg would not have any adverse effects on bone loss.

Low physiologic doses of cortisol (<15 mg) carry little risk and have a risk/benefit ratio that compares favorably to treatments that are considered standard therapies for CFS and FM, including antidepressants, NSAIDS, muscle relaxants and low-dose narcotics. For instance, there is considerable anecdotal evidence supporting the use of SSRI's in CFS and FM, and most physicians feel they are significantly beneficial in these patients. However, randomized blinded placebo controlled trials have consistently shown little benefit, with the majority of patients noting significant side effects with up to a third of patients having to discontinue treatment due to side effects (4,5). The newer dual acting antidepressants such as duloxetine have been shown to be beneficial in FM but suffer from poor tolerability (6,7). A randomized controlled trial demonstrated that duloxetine was of benefit in women with FM but not in men. In addition, 90% of patients had significant side-effects in the treatment group and 44% had to discontinue treatment due to moderate or severe side-effects (6,7).

In contrast, side effects are very rare and significant side effects are essentially non-existent with physiologic doses of cortisol. An even more compelling argument can be made when the considerable risks, that include death, of other common treatments for CFS and FM, including NSAIDS, muscle relaxants and low dose narcotics, are compared to the negligible risk of physiologic doses of cortisol.

Summary

There is ample evidence that there is HPA axis dysfunction of central origin in CFS and FM but the exact level or levels of dysfunction are less clear. The data is consistent with mixed hypothalamic-pituitary dysfunction in CFS and FM with CFS having more pituitary dominant dysfunction while FM patients have more hypothalamic or supra-hypothalamic dominant dysfunction. This is consistent with the fact that the hypothalamus has significant pain modulating properties and hypothalamic dysfunction has been shown to increase pain sensation (178).

The HPA axis is an incredibly complex group of specialized neuronal tissue, with the hypothalamus being the most complex part of the CNS. The hypothalamus consists of somewhat arbitrarily defined regions and nuclei that include the pariventricular, arcuate, suprachiasmatic, anterior, ventromedial, dorsomedial, posterior and supraoptic nuclei with extensive interaction with different afferent and efferent pathways from the thalamus, basal ganglia, cerebral cortex, reticular formation and visceral centers of the brainstem. The reticular formation and visceral centers of the brainstem connect with the hypothalamus through the mammillary peduncle and the dorsal longitudinal fasciculus. There is also significant input via locus ceruleus, vagal nuclei, periaqueductal gray and nuclei of the solitary tract and from the piriform cortex and amygdala, olfactory nuclei and the hippocampus. While the studies clearly support HPA dysfunction at the pituitary and hypothalamic levels, it is not surprising that the precise level and mechanism is unclear.

Potential mechanisms occurring in CFS include pituitary dysfunction with hyporesponsive pituitary corticotrophs, enhanced negative feedback and/or deficient hypothalamic secretion of CRH. FM patients have more dysfunction at the hypothalamic level or have abnormal hypothalamic input along with hyporesponsive adrenals to ACTH. There is convincing evidence of central regulation of adrenal sensitivity to ACTH (179). Interestingly, depressed patients are characterized by hyperactivity of all components of the HPA axis, including increased sensitivity to ACTH by the adrenals and increased CRH mRNA expression, with resultant hyercortisolism. Given the complexity of neuronal interaction in this system, it is unlikely that the precise nature of HPA axis dysfunction in CFS/FM patients will be elucidated in the near future. This certainly does not mean these patients should not be treated until such understanding is complete.

Conclusion

There is a complex interaction of HPA axis dysfunction in these patients, and it is becoming clear that the majority of patients with CFS and FM suffer from clinically significant adrenocortical dysfunction. Current methods of testing are very poor at assessing the area of dysfunction in these complex interactions, but despite this, all studies utilizing IST, CRH and/or metyrapone testing have shown abnormal results in these patients. Studies that utilize 24-hour urinary cortisol levels have consistently shown HPA axis dysfunction with only a few studies showing normal levels in CFS and FM patients. On the whole, ACTH stimulation testing has shown to be abnormal in about 50% of CFS/FM patients. This would be the expected percentage if 100% of the patients had HPA axis dysfunction of central origin, as this test suffers from very poor sensitivity for central HPA axis dysfunction and would be expected to miss approximately 50% of these patients. In addition, the inaccuracy of the most commonly used cortisol assay further confounds results. The ACTH stimulation test has clearly been shown to lack sufficient

sensitivity to differentiate CFS and FM patients with HPA axis dysfunction from those with normal function. A normal result cannot be used with any confidence in these patients to rule-out significant dysfunction; thus, it cannot be recommended as a useful test to guide treatment in these patients. The more central acting stimulation tests are also not recommended for routine clinical use because interpretation is problematic, they are burdensome and expensive and carry significantly more risk than the most appropriate treatment, a therapeutic trial of physiological doses of cortisol.

Physiologic replacement of cortisol at doses of 5-15 mg/day have been shown to be safe, with little or no associated risk, and have the potential for significant clinical benefit. Cortisol treatment carries significantly less risk and a greater potential for benefit than treatments considered to be the standard of care in the treatment of CFS/FM, including antidepressants, muscle relaxants and narcotics. The current evidence supports the use of physiologic doses of cortisol as an appropriate component of a multi-system treatment protocol for CFS and FM, and a therapeutic trial of cortisol should be considered in the majority of these patients, especially those with signs or symptoms consistent with adrenal dysfunction, low blood pressure and/or serum levels that are low or in the low normal range.

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