

Mild Adrenocortical Deficiency and its Relationship to: (1) Chronic Fatigue Syndrome; (2) Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum; and (3) Systemic Lupus Erythematosus

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Abstract *When the mind and body are challenged by stressors, the hypothalamic-pituitary-adrenal axis is stimulated, culminating in the secretion of glucocorticoid hormones, principally cortisol, by the adrenal cortex. When an individual experiences chronic stress that strains his adaptive mechanisms, it is possible that this individual might manifest clinical signs and symptoms reflective of mild adrenocortical deficiency (MAD); a condition or syndrome characterized by a chronic deficiency of cortisol, but not severe enough to result in Addison's disease. MAD is characterized by a diverse amount of clinical signs and symptoms, such as fatigue, nervousness and irritability, mental depression, postural hypotension, and hypoglycaemia. Given the sheer number of clinical features associated with MAD, it is likely that compromised adrenocortical function plays a role in the chronic course of many medical conditions. MAD is postulated to play a more dominant etiopathologic role in chronic fatigue syndrome, hyperemesis gravidarum, nausea and vomiting of pregnancy, and systemic lupus erythematosus. Several specific orthomolecular treatments, i.e., low-dose cortisol, vitamin C, and pantothenic acid, are discussed in relation to their ability to normalize adrenocortical function and possibly to improve outcomes in these respective medical conditions. More formal studies are needed, but given the safety of these substances, when used in orthomolecular doses, a therapeutic trial should be undertaken before resorting to more aggressive treatment.*

Introduction

When the mind and body are challenged by stressors, a complicated cascade of physiological events ensues as the body strives to restore homeostasis. One system in particular is stimulated, i.e., the hypothalamic-pituitary-adrenal (HPA) axis, culminating in the secretion of glucocorticoid hormones, prin-

cipally cortisol, by the adrenal cortex.¹ When an individual experiences chronic stress that strains his adaptive mechanisms, it is possible that this individual might manifest clinical signs and symptoms reflective of mild adrenocortical deficiency (MAD),² a condition or syndrome characterized by a chronic deficiency of cortisol but not severe enough

to result in Addison's disease (AD).

In 1955, Tintera published a report in which he identified the most common clinical features of hypoadrenocorticism (i.e., MAD) based on 15 years of clinical experience involving 200 patient cases (Table 1, below).³ He believed hypoadrenocorticism

to be a subclinical form of AD. Tintera reckoned that the clinical features of MAD were reflective of adrenocortical dysfunction due to either a lack of adequate adrenocortical hormone production or to some imbalance among these hormones.

In 1996, Jefferies also enumerated the

Table 1. Clinical Features of Hypoadrenocorticism

Chief Complaints	Percentage Frequency
Fatigue (excessive)	94
Nervousness and irritability	86
Mental depression	79
Apprehensions	71
Weakness (excessive)	65
Light-headedness	47
Faintness or fainting spells	42
Insomnia	40
Most Common Systemic Symptoms	Percentage Frequency
Premenstrual tension	85
Craving for salt	84
Inability to concentrate	77
Craving for sweets	75
Headache	68
Alcohol intolerance	66
Fears and apprehensions	65
Confused intervals	61
Poor memory	59
Feelings of frustration	56
Epigastric distress	51
Backaches	48
Food or drug idiosyncrasies	47
Alternate diarrhoea and constipation	45
Indigestion	40
Anorexia	34
Findings on Physical Examination	Percentage Frequency
Postural hypotension	93
Generalized cervical lymphadenitis	93
Skin thin and dry	91
Perspirations scanty	91
Hair sparse	83
Asthenic habitus	78
Positive Rogoff sign	71
Redness of thenar and hypothenar eminences	28
Blanching on exposure to cold	21

in fatigue between both groups. There were also no between-group differences on other measurements, so the authors concluded that combination therapy of low-dose cortisol and fludrocortisone was not effective in patients with CFS. Questions have been raised about the patients selected for inclusion in this study since they were recruited from a tertiary care university hospital, and many of them had fatigue-related illnesses in addition to CFS.³ These results, therefore, should not be used to refute the potential value of low-dose cortisol for CFS.

Other studies have been done using physiological doses of cortisol as part of an integrative approach to treating fibromyalgia (FM) and CFS. Teitelbaum et al conducted a randomized, double-blind, placebo-controlled, intent-to-treat study on 72 FM patients (38 active and 34 placebo patients; 69 patients met CFS criteria).²⁷ The active patients received an integrated approach that included physiological doses of cortisol (usual dose: 5-12.5 mg/day; maximum dose: 20-25 mg/day). Cortisol was administered to 29 of the 38 patients at some point during the three month study based on specific biochemical results and/or if they had three symptoms consistent with adrenal dysfunction (e.g., sugar craving, shakiness relieved by eating, and dizziness). The results showed significant improvements compared to placebo in visual analog (well-being) scores ($p < 0.0002$), the Fibromyalgia Impact Questionnaire ($p < 0.0005$), the Tender Point Index ($p < 0.0001$), and overall response ($p < 0.0001$). None of the patients had evidence of adrenal suppression following post-treatment ACTH stimulation. Even though this study relied on an integrative approach, the results do suggest that physiological (i.e. low) doses of cortisol in conjunction with numerous other treatments can significantly benefit patients with CFS.

Holtorf also uses an integrative approach when treating CFS and FM.⁴ His centre has tracked over 500 patients meeting CDC criteria for CFS and/or American College of Rheumatology criteria for FM. Two-hundred and forty of his patients

have both disorders. He gives patients physiological doses of timed-release cortisol (5-15 mg/day) following their second visit if they have symptoms consistent with adrenal dysfunction based on 24 symptoms and/or low blood pressure and/or having baseline cortisol in the low or low-normal range. In addition, patients are administered fludrocortisone if they have symptoms consistent with neutrally-mediated hypotension. Analysis of his data has shown that 94% of patients improve overall by the fourth visit, with 75% having significant overall improvement, and 62% having substantial overall improvement. The clinical difference between "significant" overall improvement from "substantial" overall improvement was not delineated. Over the course of treatment, patients continued to improve at subsequent visits. Energy levels and sense of well-being increased from their respective baseline scores of 2.98 and 3.03, to 7.67 and 6.83 by the ninth visit. Among the closely-monitored patients (number unspecified), none experienced any significant side effects from physiological doses of cortisol.

There is even a randomized, placebo-controlled, double-blind study that evaluated the merits of pharmacological doses of cortisol for the treatment of CFS over the course of 12 weeks.²⁸ Thirty patients with CFS were administered 25-35 mg/day of cortisol, and a control group of 35 patients were given placebo. Some 66.7% of the CFS patients noted improvement on a global Wellness scale compared to placebo. More specifically, there was an improvement of five or more points in the Wellness scale, and a greater average improvement on more days compared to participants in the placebo group ($p < 0.001$). On the other rating scales used, none demonstrated any statistical significance compared to placebo. For 12 patients who received cortisol, suppression or suboptimal cortisol responses to cosyntropin (i.e., ACTH) were documented demonstrating that the 25-35 mg daily doses of cortisol used in this study suppressed adrenal function. Even though there were some positive outcomes in this study, it is not typical to treat CFS patients with doses of cortisol this high.

Table 2. Clinical Similarities between CFS and AD*

General: persistent fatigue, post-exertional malaise, weakness, fever, enlarged lymph nodes, myalgia, arthralgia, flu-like symptoms, sore throat, headaches, dizziness upon standing

Psychiatric: depression, confusion, inability to concentrate, forgetfulness, irritability, sleep disturbance

Gastrointestinal: anorexia, nausea, diarrhoea, constipation

Adrenal glands and hormones: hypocortisolism, impaired adrenocortical function, reduced adrenal gland size, antibodies directed against the adrenal gland, enhanced thyroid-stimulating hormone secretion

Heart and circulation: reduction in both left ventricular dimensions, and other cardiac measures, increased heart rate, postural hypotension, orthostatic tachycardia, dehydration

Haematology: leukocytosis, lymphocytosis, raised production of cytokines

Liver: transaminitis

Muscular: respiratory muscle dysfunction

Onset and prevalence: sudden onset, over-representation of middle-aged women

*Adapted from: Baschetti R. Chronic fatigue syndrome: a form of Addison's disease. *J Intern Med*, 2000;247:737.

ized crossover trial by Cleare et al, 32 patients with CFS were given 5-10 mg/day of cortisol each morning for one month and then placebo each morning for one month, with the order of treatment being randomly assigned.²⁵ There were significant improvements in fatigue and disability among patients taking low-dose cortisol ($p=0.009$), but not when taking the placebo. Twenty-eight percent of the CFS patients normalized from treatment. IST showed no suppression of endogenous adrenal function resulting from low-dose cortisol treatment. In a follow-up study, the 28% of patients that responded to treatment were challenged with human CRH.⁹ All these patients showed a normalization of their previous blunted cortisol response

to human CRH. Cleare et al ascertained that the HPA axis disturbance, whether primary or secondary, might be one reversible factor contributing to fatigue in CFS.

Another study evaluated the therapeutic effects of 5 mg of cortisol and 50 mcg of fludrocortisone in a 6-month randomized, placebo-controlled, double-blind, crossover design.²⁶ Eighty patients completed 3-months of treatment and three months of placebo. None of the patients had any evidence of adrenal suppression from treatment. Both groups had significant improvements in their fatigue scores as per the Abbreviated Fatigue Questionnaire, but the differences were not statistically significant. The visual analog scale did not reveal any differences

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Overall, the data does suggest that the impaired ability to secrete effective amounts of cortisol might be a primary factor in the genesis of CFS; possibly, the result of HPA axis dysfunction due to problems involving the pituitary (secondary adrenocortical deficiency) or the hypothalamus (tertiary adrenocortical deficiency). There also seems to be enough data suggesting that CFS is a more mild form of AD. All of the intervention studies summarized here, while not involving huge numbers of patients, demonstrate that physiological doses of cortisol as monotherapy, or in combination with other treatments, is safe and beneficial to many patients having CFS.

Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum

Some 80% of women will experience some nausea and vomiting during their pregnancy (NVP).²⁹ Hyperemesis gravidarum (HG) is a more severe form of NVP, and is characterized by intractable vomiting leading to fluid, electrolyte and acid-base imbalance, nutrient deficiencies, and severe weight loss often requiring hospital admission.³⁰ The onset of HG occurs sometime between the fourth and tenth week of gestation, with resolution by the twentieth week even though some 10% of patients will have HG throughout pregnancy.²⁹

The pathogenesis and etiology of HG continues to be the subject of much debate. Many theories have focussed on pregnancy-related hormones (i.e., progesterone, estrogens, and human chorionic gonadotropin), leptin, placental growth hormone, prolactin, thyroid, and adrenal cortical hormones as putative underlying factors in the etiology of HG.³¹ In 1933 Kemp argued that both NVP and HG are the result of a temporary adrenal cortex insufficiency (i.e., MAD).³² Kemp based his hypothesis on several known facts about NVP and HG and their similarities to AD. He pointed out that: (1) the maternal adrenal cortex undergoes hypertrophy during pregnancy; (2) the initial symptoms of adrenal cortex insufficiency in adrenalectomized animals are anorexia and

vomiting; (3) the initial symptoms of AD in humans are anorexia and morning sickness (regardless of sex); and (4) post-mortem findings of HG are similar to necropsy findings following complete adrenalectomy in animals and to humans having died from AD.^{32,33} In Kemp's 1933 paper, he described eight cases of HG that were successfully treated with adrenal cortical extract (i.e., a crude form of cortisol derived from bovine).³² In his 1934 paper, he reported on a total of 202 cases of NVP in which 173 (85.6%) were either completely relieved of their symptoms or had definitive improvement following the use of adrenal cortical extract.³³ The most effective results were obtained by giving one to two ampules daily of the liquid adrenal cortical extract (Armour brand) subcutaneously, which normally resulted in the immediate and complete cessation of vomiting. This was then followed by the oral administration of nine to twelve grains (approximately, 585-780 mg) of desiccated adrenal cortical extract daily until the patient felt normal, which was further reduced to six grains (approximately, 390 mg) until the third month or before if the symptoms completely cleared.

The overarching support of this treatment approach, according to Kemp, is based on the increased adrenocortical demands that occur during the first trimester of pregnancy. Prior to pregnancy some women have sufficient adrenocortical function just able to meet their physiological demands. However, when these same women become pregnant they experience a temporary adrenocortical insufficiency until their adrenal cortex hypertrophies sufficiently (usually at the end of the third month) to produce adequate amounts of hormone to meet the demands of their remaining pregnancies. Thus, the therapeutic use of adrenal cortical extract merely corrects for the temporary MAD state of early pregnancy.

Since Kemp's hypothesis, numerous studies have been done to investigate the merits of using corticosteroids to treat HG. Several of these studies will be highlighted here. Wells, in 1953, observed a reduction in HG symptoms from corticosteroid therapy and used doses of cortisone as low as 25 mg with

beneficial results.³⁴ In 1996, Taylor reported on 7 women with HG using high-dose steroid therapy.³⁵ In this series, the hospitalized women were treated with 50 mg twice daily of hydrocortisone intravenously until vomiting ceased, which was within three hours for all patients. This was then followed by oral prednisolone therapy (up to 45 mg/day) until discharge from the hospital. This allowed for a return of normal eating, a reversal of muscle wasting and a regain of lost weight. The prednisolone treatment (15 mg/day or more) was taken for 10.6 ± 4.7 weeks to enable suppression of intractable HG symptoms and normal maternal nutrition. No adverse effects were observed during the remainder of the pregnancies from this treatment approach. Taylor believed that high-dose corticosteroid therapy exerted its effects by having direct effects upon a vomiting centre within the brain as opposed to correcting for any deficit of pituitary-adrenal reserve.

In 1998, Safari et al reported on the use of oral methylprednisolone treatment for refractory HG.³⁶ Eighteen patients were admitted to hospital and given intravenous thiamine (100 mg) and an intravenous glucose-normal saline solution (i.e., for hydration). They were also treated with 48 mg/day of oral methylprednisolone for three days followed by a tapering dose over two weeks. If vomiting returned following the two weeks or at any time during tapering, the dose of methylprednisolone was restarted or continued for one month or less. Seventeen of the 18 patients were free of vomiting and had a return of normal eating within three days. Seven of these patients remained symptom free during the rest of their pregnancies. Nine women had a return of vomiting during or following tapering, and seven had a full response to extending or resuming treatment. Four of six women on total parental nutrition at the onset of treatment had complete resolution with three days of treatment. The authors of this observational study concluded that brief treatment with oral methylprednisolone treatment was an effective alternative for intractable HG. They also noted that the benefits of this treatment

might be the result of its actions upon the “chemotherapy trigger zone” within the brain stem. However, they also mentioned the work of Kemp and his “relative adrenal insufficiency” hypothesis since the AD-like symptoms develop due to the inability of the HPA axis to respond adequately to the “increased demands for adrenal output in early pregnancy.”

A more formal study by Safari et al was published later in 1998 and compared the efficacy of methylprednisolone to that of promethazine for the treatment of HG among patients admitted to hospital.³⁷ Forty patients were randomized to receive either oral methylprednisolone (16 mg three times daily; $n=20$), or oral promethazine (25 mg three times daily; $n=20$) for up to two weeks. Patients in the methylprednisolone group were able to taper completely over a two week period after being on the treatment for three days, whereas patients in the promethazine group needed to take this intervention for the full two weeks. Seventeen patients from each group who were discharged also had adequate follow-up information to report on. None of the 17 patients in the methylprednisolone group were readmitted to hospital following discharge, but five of the 17 in the promethazine group were readmitted ($p=0.001$). No adverse effects were noted for each treatment. The results demonstrated that a short duration of methylprednisolone was more effective than promethazine for the treatment of HG. Once again these authors cited the work of Kemp to support this treatment approach, but noted that they used pharmacologic doses, which did not therefore evaluate and validate Kemp’s hypothesis.

A more recent study published in 2012 by Tufail et al compared steroid therapy to dimenhydrinate in patients with HG between 10 and 20 weeks gestation.³⁸ Fifty patients received intravenous hydrocortisone (100 mg every 8 hours) for three days, followed by 45 mg/day of oral prednisolone which was tapered off in five days. Another fifty patients received 50 mg of intravenous dimenhydrinate for three days, followed by 50 mg three times daily of the same medica-

tion taken orally for five days. All patients were followed during treatment and for two weeks following discharge. The results showed a significant reduction in vomiting from the steroid group compared to the dimenhydrinate ($p < 0.0001$). None of the patients in the steroid group were readmitted, but eight of the patients in the demenhydrinate group were. The authors of this study did not discuss why this treatment was effective, but simply noted that steroid therapy after the tenth week of gestation did not cause maternal or foetal deleterious complications.

Two of the modern reports about HG described in the preceding text discussed the "relative adrenal insufficiency" hypothesis and suggested that the favorable responses they observed might have been the result of offsetting the relative deficiency of cortisol that occurs early in pregnancy. None of these modern reports used physiological doses of cortisol as a treatment approach. Kemp's work showed that physiological doses of adrenal cortical extract possess therapeutic value in keeping NVP from progressing to HG. For patients that progress to HG, high-dose steroid therapy appears to be indicated based on the best and most current available evidence. It appears more likely that physiological doses of cortisol when given during the first trimester of pregnancy might serve to prevent the onset of HG, and thus eliminate the need to resort to hospital admission and high-dose steroid therapy. Given the possibility that early pregnancy does represent a state of "relative adrenal insufficiency," the use of physiological doses of cortisol to prevent HG should be more formally studied.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) "is a chronic, multisystem, inflammatory disorder of autoimmune etiology, occurring predominantly in young women. Common manifestations may include arthralgias and arthritis; malar and other skin rashes; pleuritis or pericarditis; renal or CNS involvement; and hematologic cytopenias."³⁹ The immune system derangement that accompanies SLE

results in excessive helper T-cell activity, insufficient T-suppressor activity, and abnormal cell signaling that leads to polyclonal B-cell proliferation and the formation of autoantibodies.⁴⁰

Although the cause is unknown, there is some evidence that SLE might be linked to a deficiency in coenzyme A (CoA). CoA is essential to the synthesis of cholesterol, all sex hormones, and corticosteroids. The leading proponent of this hypothesis is Dr. Lit-Hung Leung, who has articulated in several publications the notion that a deficiency in coenzyme A (CoA) might be involved in the pathogenesis of SLE based on several known facts about the disease.^{41,42}

1. That the disease favours females because of the increased demand for sex hormones that occurs around the time of puberty. During puberty, the demand for CoA increases because of the increased demand for sex hormones, and, in some susceptible females, this gives rise to symptoms of CoA deficiency (and eventually, SLE) because the body's CoA needs are not being adequately met.

2. This CoA deficiency state leads to reproductive problems common in SLE, which increase with each menstrual cycle as women go from puberty to menopause, and are marked by lower estrogen and progesterone levels, and higher follicle stimulating and luteinizing hormone levels. These hormone deficiencies manifest clinically as late menarche, irregular menses, amenorrhea, and early menopause. These hormone deficiencies also result in flares premenstrually and during pregnancy since these instances are marked by increased demands for sex hormones, which cannot be met owing to depleted or exhausted CoA reserves.

3. This deficiency in CoA also leads to low levels of corticosteroids (i.e., cortisol and dehydroepiandrosterone), which are common among patients having SLE, and are significantly lower when compared to controls. This is clinically important since SLE patients benefit from medications that either spare cortisol (hydroxychloroquine) and/or increase the amount of cortisol (prednisone) that is present in the human body.

4. When SLE patients are under increased psychological/emotional stress, they are unable to generate a sufficient amount of cortisol, which often causes these patients to experience a flare-up.

To correct this deficiency state, the therapeutic use of high-dosages of pantothenic acid would be necessary, as it increases CoA levels and provides the necessary building blocks for the synthesis of all sex hormones and corticosteroids. The consequences of this would be symptoms of MAD (due to a deficiency of cortisol) in addition to symptoms reflective of sex hormone deficiency.

To test this hypothesis, Leung administered high-doses of pantothenic acid, along with other nutrients, to 12 female patients (age range 18-43) having SLE (Table 3, below).^{41,42} Leung reasoned that SLE patients are more likely to have multiple nutrient deficiencies since the unpredictable clinical picture in SLE would most likely represent a “combined deficiency syndrome” associated with diverse clinical manifestations arising from multiple nutrient deficiencies. Pantothenic acid, however, would be the most important of all nutrients needed by SLE patients.

Patients were reassessed every 4-6 weeks for 1-2 years. All patients showed varying degrees of improvement, particularly in their symptom of fatigue. Later follow-up showed that the incidence of fever was reduced and no major flares were noted during the period of observation. In the majority of cases, the original SLE medications could gradually be reduced.

Even though SLE would not be considered a purely “MAD” issue, patients with

this disease manifest many symptoms reflective of MAD as a result of their inability to produce adequate amounts of cortisol. Jefferies noted that patients with any autoimmune disease (including SLE) experience exacerbations following sufficient stress, and that they might improve from small, physiological dosages of cortisol with temporary increases during times of stress.⁴³ Thus, it seems reasonable to view SLE as being a variant of MAD even though the more central issue (if Leung’s theory is correct) is a deficiency in CoA secondary to a deficiency in pantothenic acid.

Orthomolecular Treatment Considerations

Based on the data reviewed here, patients having CFS, SLE or NVP should be given an empiric trial of 2.5-5.0 mg of cortisol four times daily (i.e., with each main meal and at bedtime). The cortisol can either be prescription hydrocortisone, or can be a plant-derived source (known as Isocort™; see: <http://www.bezwecken.com/>) which provides around 2.45 mg of cortisol per pellet. If patients are provided with Isocort™, they would need to take 1-2 pellets (approximately, 2.45-4.90 mg) four times daily. Should patients with CFS or SLE experience an exacerbation or symptoms of an impending acute infection (e.g., sore throat and nasal congestion), they should be instructed to double their dose, and maintain it until the exacerbation or symptoms of an impending acute infection have passed. Once passed, the initial dose should be resumed. For patients with NVP, the use of cortisol should be reserved for the

Table 3. Daily Nutrient doses used in Leung’s Study

Pantothenic Acid	10 g
Vitamin C	2 g
Vitamin B ₁	500 mg
Vitamin B ₆	200 mg
Vitamin B ₁₂	2 mg
B-Complex	2 tablets
Multiple vitamin/mineral supplement	2 tablets

first trimester only, and would not need to be taken throughout the entire pregnancy.

In addition to cortisol replacement, it might also be prudent to supply ample amounts of vitamin C to patients with CFS, NVP, and SLE. The adrenal cortex and the medulla accumulate very high levels of vitamin C, and the vitamin functions as a required cofactor in both catecholamine biosynthesis and adrenal steroidogenesis.⁴⁴ A clinical trial involving 120 healthy men also showed 1,000 mg of sustained-release vitamin C given three times daily to moderate stress and increase salivary cortisol recovery.⁴⁵ Klenner also reported that during pregnancy the body has increasing demands for the vitamin as the gestational period proceeds from the first trimester, to the second, and finally to the third (approximately, 4 g/day, 6 g/day, and 10 g/day respectively).⁴⁶ He even commented on the robustness of the infants born to mothers having taken large doses of the vitamin. There is even a study that assessed very small oral doses of vitamin C (25 mg/day) in combination with vitamin K (as menadione bisulfate; 5 mg/day) among 70 patients with NVP.⁴⁷ Sixty-four patients taking this combination experienced complete remission within 72 hours. The author postulated that both vitamins counteract increased capillary permeability in the placental base, thus mitigating some proposed "vomiting factor" being transferred from the placenta or foetal circulation to the expectant mother. It is also possible that vitamin C lessened some of the additional burden imposed upon the adrenal cortex that occurs early in pregnancy. A higher daily dose of vitamin C would likely produce more significant and perhaps quicker results among women having NVP, but more formal and rigorous studies are needed to confirm this application of the vitamin. It makes sense, therefore, to support the adrenal gland's production of cortisol by prescribing at least 1,000 mg three times daily of sustained-release vitamin C to all patients with these three medical conditions.

Consideration should also be made with respect to the use of pantothenic acid for

CFS, NVP, and SLE. In a study in which pantothenic acid deficiency was induced in normal young adult men, symptoms of adrenal insufficiency developed and the subjects had to be given small daily doses of cortisone for four days to overcome this crisis.⁴⁸ Three days following cortisone administration, the subjects returned to normal by eating the original synthetic liquid diet containing pantothenic acid. In a 1947 publication, Kemp cited additional research noting the advantages of taking pantothenic acid with adrenal cortical extract since normal adrenocortical function is dependent on the vitamin.⁴⁹ He recommended 650 mg of pantothenic acid to be used alongside adrenal cortical extract for preventing and treating NVP. Although the exact relationship between pantothenic acid and adrenal function has not been fully elucidated, it does seem possible that therapeutic doses of the vitamin would benefit patients having symptoms reflective of MAD. Patients with NVP would not require very large doses during the first trimester, but should be offered 1 g/day while they are also taking physiological doses of cortisol. Patients with CFS and SLE should take 10 g/day of pantothenic acid based on the work of Leung.^{41,42} Side effects with pantothenic acid are rare, but some individuals might experience frequent bowel movements (or even diarrhoea) from the vitamin due to its ability to stimulate peristalsis. Patients should be warned of this possibility.

Conclusion

I have attempted to describe the clinical features of MAD and the medical conditions for which MAD might be an etiopathologic factor. I have highlighted the importance of cortisol, and how a subtle deficiency in its production might undermine recovery from CFS, NVP, and SLE. There also appears to be some literature demonstrating efficacy from using physiological doses of cortisol (15-20 mg/day) or multi-gram doses of pantothenic acid (to increase CoA) to reduce the clinical manifestations of MAD as expressed in these respective medical conditions. Therapeutic doses of vitamin C should also be prescribed

because ascorbic acid is an essential factor in normal adrenal function. More formal studies are needed, but given the safety of these orthomolecular substances, when treating patients with mild adrenocortical deficiency, a therapeutic trial could be undertaken before resorting to more aggressive treatment.

Acknowledgements

I thank Mr. Bob Sealey for his helpful editing suggestions and input on the contents of this paper.

Competing Interests

Dr. Prousky is currently a consultant for Pascoe Canada, a company that sells natural health products.

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