Nutritional Strategies for Treating Chronic Fatigue Syndrome

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Abstract
Despite considerable worldwide efforts, no single etiology has been identified to explain the development of chronic fatigue syndrome (CFS). It is likely that multiple factors promote its development, sometimes with the same factors both causing and being caused by the syndrome. A detailed review of the literature suggests a number of marginal nutritional deficiencies may have etiologic relevance. These include deficiencies of various B vitamins, vitamin C, magnesium, sodium, zinc, L-tryptophan, L-carnitine, coenzyme Q10, and essential fatty acids. Any of these nutrients could be marginally deficient in CFS patients, a finding that appears to be primarily due to the illness process rather than to inadequate diets. It is likely that marginal deficiencies not only contribute to the clinical manifestations of the syndrome, but also are detrimental to the healing processes. Therefore, when feasible, objective testing should identify them and their resolution should be assured by repeat testing following initiation of treatment. Moreover, because of the rarity of serious adverse reactions, the difficulty in ruling out marginal deficiencies, and because some of the therapeutic benefits of nutritional supplements appear to be due to pharmacologic effects, it seems rational to consider supplementing CFS patients with the nutrients discussed above, along with a general high-potency vitamin/mineral supplement, at least for a trial period.
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Introduction

The disorder we call chronic fatigue syndrome (CFS) does not appear to be new. The current interest in attempting to define and treat it stems from several studies in the mid-1980s that found elevated levels of antibody to Epstein-Barr virus in people with CFS-like symptoms, most of whom had had a history of infectious mononucleosis a few years earlier.

When it later became apparent that healthy people could also have elevated Epstein-Barr virus antibody titers while some CFS sufferers had normal titers, the U.S. Centers for Disease Control and Prevention developed a research case definition that defined the syndrome by its most common presenting characteristics. In 1994, the International CFS Study Group published a revised and more inclusive case definition[1] which defines chronic fatigue syndrome. See Table 1.

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Table 1: International CFS Study Group Definition of Chronic Fatigue Syndrome

I. Clinically evaluated, unexplained persistent or relapsing chronic fatigue that:
- is of new or definite onset (has not been lifelong).
- is not the result of ongoing exertion.
- is not substantially alleviated by rest.
- results in substantial reduction in previous levels of occupational, educational, social, or personal activities.

II. The concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during six or more consecutive months of illness and must not have predated the fatigue:
- self-reported impairment in short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities
- sore throat
- tender cervical or axillary lymph nodes
- muscle pain
- multi-joint pain without joint swelling or redness
- headaches of a new type, pattern, or severity
- unrefreshing sleep
- postexertional malaise lasting more than 24 hours

Despite considerable worldwide efforts, no single etiology has been found to explain the syndrome. It is likely that multiple factors promote its development, sometimes with the same factors both causing and being caused by the syndrome. Many of these factors constitute specific pathophysiological entities that characterize certain subsets of chronic fatigue patients. See Table 2. Numerous factors appear to promote the development of the syndrome. See Table 3.

This review of the nutritional literature focuses on those nutrients for which the evidence most strongly supports relevance to treatment. The scientific literature is fairly sparse, and promising nutritional treatments usually lack adequate scientific proof. For these reasons, in addition to examining studies of CFS patients, this review will also focus on studies of patients presenting with individual aspects of the syndrome, such as fatigue or an impaired immune response to viral infections.

Vitamins for Treatment of Chronic Fatigue Syndrome

Folic Acid

A subset of CFS patients appears to be deficient in folic acid. Based on established norms, half of a group of 30 male and 30 female patients had deficient serum folate concentrations, while another 13 percent had low-borderline concentrations.[2] What makes this finding particularly interesting is the fact that serum folate is highly correlated with the folate level of the cerebrospinal fluid. While erythrocyte folate is usually a better indicator of folate deficiency,[3] serum folate is a better indicator of cerebrospinal fluid folate.[4] Although the brain maintains adequate folate levels longer than most tissues,[4] a chronically low serum folic acid level – and thus a chronically low cerebrospinal fluid folic acid level – would be a reasonable basis for suspecting that brain folate could be diminished in CFS, causing impairment in brain function.

Table 2: Suspected Etiologies for Chronic Fatigue Syndrome

Viral infections and the post-viral fatigue syndrome
Fibromyalgia
Neurally-mediated hypotension
Psychogenic biological dysfunction
Low natural killer cell syndrome

Is this consistent with the clinical presentation? Fatigue and depression, common findings in CFS, are also prominent features of folate deficiency.[5] Moreover, several experimental studies found folate supplementation to be effective for improving mood in folate-deficient members of the general population.[5,6] Folate deficiency can cause immunodepression, and CFS often presents with evidence of immune activation, so the contribution of a marginal folate deficiency to the immunological picture in CFS should be considered unknown until it is formally studied.

While we can surmise that folate supplementation would be effective in chronic fatigue patients with a marginal folate deficiency, its efficacy in this population has been investigated only in a small, double-blind crossover study that failed to find benefits from supplementation with daily, intramuscular injections of 800 mcg of folate for one week.[7] It should be noted that the study was of very short duration. In addition, this dosage, although often considered adequate to correct a folate deficiency, is small when compared to the folate dose used in another study to successfully treat a group of patients who, although they did not have CFS, presented with easy fatigability and minor neurological signs. These patients received a minimum of 10,000 mcg of folate daily, yet it took two to three months for their fatigue to respond.[8] Therefore, if folic acid supplementation is effective in CFS, it is possible that substantially larger dosages will have to be prescribed for a substantially longer period of time.

Vitamin B12

In an informal study of more than 100 CFS patients, 30 percent showed elevations of methylmalonic acid,[9] a urinary metabolite believed to be considerably more sensitive than serum vitamin B12 for diagnosing cobalamin deficiency.[10] Moreover, a study of 12 women who fulfilled the criteria of both CFS and fibromyalgia found the levels of vitamin B12 in the cerebrospinal fluid were significantly correlated with measures of fatigability and neurasthenia.[11]

Is a B12 deficiency consistent with the presentation of chronic fatigue syndrome? As in the case of folic acid, fatigue and depression are features common to both disorders,[5,12]

Table 3: Factors Suspected of Promoting Chronic Fatigue Syndrome

Hypoxemia
Endocrine dysfunction
Immune dysfunction
Stress-related dysfunction
Somatoform disorder
Marginal nutritional deficiencies
Intestinal hyperpermeability
Overgrowth of pathogenic intestinal flora (dysbiosis)
Food and chemical sensitivities
Chemical toxicity
Heavy metal toxicity

suggesting inadequate B12 nutriture could contribute to the clinical picture in a subset of patients.

Also, as already noted in regard to folic acid, there is no scientific data proving the efficacy of vitamin B12 supplementation in CFS patients. There is data supporting the theory that the vitamin, given by injection, is therapeutic. Similar to the situation with folic acid, these data suggest the total dose of B12 necessary for a response is massive when compared to the dose considered adequate to correct a B12 deficiency.

An accepted regimen for treating vitamin B12 deficiency is to initially administer 1000 mcg of the vitamin IM weekly. The patient usually responds rapidly, and the dose is then decreased to 1000 mcg each month for as long as needed.

Lapp and Cheney shared their observations from treating more than 2,000 patients in a clinical setting. Initially, they administered relatively small amounts of vitamin B12, but the results were inconsistent, so the dosage was increased to 2,500-5,000 mcg cyanocobalamin (subcutaneous or IM) every two to three days. Fifty to eighty percent eventually responded with an increase in energy, stamina, or well-being, usually within two to three weeks of treatment.[9,13]

Although these results are promising, the same double-blind crossover study alluded to earlier in regard to its failure to find folate supplementation to be effective, also failed to find evidence that vitamin B12 supplementation provided anything more than a placebo effect. In this instance, the CFS patients received daily intramuscular injections of 2 ml of a solution containing 200 mcg cyanocobalamin or placebo for one week.[7] Since, however, the dosage utilized was less than one-quarter of the minimal effective dosage in Lapp and Cheney's report, the question of the efficacy of higher dosages for treating depression and fatigue in this disorder arguably remains unanswered.

Some additional data comes from two studies of people who felt poorly but had not been specifically diagnosed as having chronic fatigue syndrome or any other specific disorder. The first, a double-blind crossover study, concerned men and women who complained of chronic tiredness but had no physical findings and normal serum B12 concentrations. They received intramuscular injections of 5,000 mcg of vitamin B12 or placebo twice daily for two weeks, each in random order with a two-week rest period in between. The vitamin injections resulted in a significant increase in feelings of well-being. The placebo injections had no effect, so long as placebo was given first. If, however, vitamin B12 was given first, there was no change between the B12 and the placebo period, suggesting the effect of the vitamin lasted at least four weeks.[14]

An informal study found a substantial proportion of patients with normal serum B12 concentrations felt better following injections of hydroxocobalamin but not following injections of sterile water. The maximum feeling of well-being, which was established through open trials, occurred using dosages ranging from 3000 mcg four times weekly to 9000 mcg daily.[15]

In comparing the total weekly dosages of vitamin B12 in the four studies, it is arguable that the dosage of the only negative study was so low that the study failed to disprove the hypothesis that administration of higher vitamin dosages may be an effective treatment intervention.

A substantial amount of vitamin B12 appears to be necessary to relieve the symptoms of CFS, compared to the amount needed to correct a B12 deficiency; thus, the vitamin appears to exert a pharmacologic effect. As a drug, vitamin B12 seems to have substantial analgesic properties. Indeed, in open trials, patients with vertebral pain syndromes,[16] degenerative neuropathies,[17] and cancer[17] noted excellent pain relief with injections of 5,000 to 10,000 mcg daily.

While analgesia achieved in open trials may be attributed to the placebo effect, rat experiments have offered some objective confirmation. Using an animal model of pain, not only did orally-administered vitamin B12 have an analgesic effect, but the effect was dose-dependent.[18] Thus, the improved feelings of well-being in CFS patients following vitamin B12 supplementation could be at least partly due to the analgesic effect of the vitamin when administered at pharmacologic dosages.

A very interesting theory proposes a mechanism by which B12 pharmacotherapy may reduce CFS symptoms. Both Mukherjee and Simpson have provided evidence that CFS symptoms are associated with an increased percentage of abnormally-shaped erythrocytes (non-discocytes).[19-21] Mukherjee has found that, in CFS sufferers, 40-100 percent of their erythrocytes are grossly deformed and can be identified as rigid stomatocytes and dimpled spherocytes.[22]

Erythrocytes normally measure eight microns in diameter, while the diameter of the vessels through which they flow may be only three microns. Mukherjee and Simpson have each postulated that loss of the normal biconcave form impairs the ability of erythrocytes to change shape in order to traverse the microcirculation. The result is a reduction in blood flow on the microcirculatory level, causing an oxygen deficit and an accumulation of by-products of cellular respiration. This pathophysiological change could help to explain why CFS patients often present with symptoms referable to multiple organ systems.

In an open trial, Simpson administered 1,000 mcg cyanocobalamin intramuscularly to a group of patients with myalgic encephalomyelitis who also exhibited an increased percentage of non-discocytes. Half of the patients noted an improved sense of well-being within 24 hours and their improvement was found to correlate with a reduction in non-discocytes. By contrast, patients who failed to improve showed no change in red cell shape. The author has suggested that vitamin B12 administration may relieve CFS symptoms by reversing the erythrocyte abnormalities leading to improved tissue oxygenation.[23]

Other B Vitamins

Other B vitamins for which there is evidence of reduced nutriture in CFS include riboflavin,[24] thiamine,[24-26] and pyridoxine.[24] While niacin nutriture in this disorder has not been studied, there is evidence that supplementation with nicotinamide adenine dinucleotide (NADH), the reduced coenzyme form of the vitamin, may be beneficial. In a double-blind crossover study, 10 mg daily of the reduced form of NADH was significantly more effective in reducing symptoms than placebo. Moreover, these patients were found to have elevated urinary concentrations of 5-hydroxy-indoleacetic acid, the major metabolite of the neurotransmitter serotonin, and the concentrations returned to normal following NADH supplementation.[27,28]

Vitamin C

Depression is the first symptom of experimental scurvy,[29] and a marginal deficiency of vitamin C may cause fatigue, lassitude, and depression[30] which responds to supplementation.[5,31] Although an early report failed to find evidence of decreased serum ascorbate levels in CFS patients,[25] no current assay technique for ascorbic acid is entirely satisfactory[32] and therefore this single report of serum ascorbate levels arguably does not eliminate the possibility that a subset of CFS patients is vitamin C-deficient.

Since vitamin C deficiency causes capillary fragility, perhaps the best method of assaying vitamin C stores is to perform the Rumpel-Leede test in which a tourniquet is applied to the arm for five minutes to see whether petechiae appear.[33] As to assay techniques, the best is probably the ascorbic acid

saturation test which measures the body's efforts to conserve vitamin C following a loading dose.[34] Data on the results of these tests in CFS has yet to be reported; therefore, the issue of whether vitamin C is marginally deficient in a subset of patients remains unsettled.

Like vitamin B12, ascorbic acid appears to exert a substantial analgesic effect at pharmacologic dosages. In a double-blind crossover study, supplementation of normal volunteers with 1 gm vitamin C three times daily reduced delayed-onset muscle soreness following strenuous exercise.[35] Under double-blind conditions, severely ill cancer patients receiving 10 grams daily experienced a significant reduction in pain[36] while, in an open trial, 10 grams daily reduced the sensitivity of teeth to air and water.[37] However, whether the analgesic effects of ascorbic acid supplementation extend to patients with chronic fatigue syndrome is not known.

Results of a study published only in abstract form suggest vitamin C supplementation may also share with vitamin B12 the ability to reverse erythrocyte membrane abnormalities seen in CFS and thus improve capillary blood flow. Using high resolution, phase contrast microscopy, 25 chronically disabled CFS patients were all found to exhibit two or more membrane abnormalities in over half of their red cells, while only 10 percent of red cells of the control subjects hospitalized for elective surgery met this criterion.[38,39] They received an intravenous infusion containing 15 grams of ascorbic acid. Fifteen minutes later, postinfusion blood samples showed that over 80 percent of the membrane abnormalities had disappeared. Moreover, based on changes seen in colliding cells, there was a higher degree of pliability in the cell wall.[38,39] Whether these findings coincided with clinical improvement was not reported.

Vitamin C supplementation also bolsters immune responses. Normal volunteers supplemented with 1-3 grams vitamin C daily showed enhanced immune function, including increased neutrophil motility[40] and chemotaxis,[41] increased immunoglobulin levels,[42,43] and increased lymphocyte blastogenesis in response to mitogens.[41] In persons with recurrent infections due to primary defects of phagocytic function, vitamin C is considered to be the specific therapy.[44] Vitamin C has considerable antiviral activity which may be due, at least in part, to enhanced interferon activity.[45] However, in CFS, ability of vitamin C to normalize immune responses or to bolster antiviral defenses is unknown.

Minerals

Magnesium

Stress hormones, including both catecholamines and corticoids, can promote a reduction in tissue magnesium levels.[46] Seelig noted that many of the symptoms and findings in CFS resemble those of magnesium deficiency.[46] See Table 4.

Several studies of magnesium nutriture in CFS have been published. The findings have been mixed,[25,26,47-52] although two studies published in major peer-reviewed journals found lower erythrocyte magnesium levels in CSF patients than in controls.[25,51] See Table 5.

Among patients seen in clinical settings, magnesium deficiency appears to be common. For example, a referral center that evaluated several hundred CFS patients noted half of their patients were magnesium-deficient.[26] Testing for magnesium retention following a magnesium load is a more sensitive assay than simply examining blood or urine levels. Specifically using this test, 45 percent of a group of 97 patients were found to be magnesium-deficient,[53] while an unpublished study found evidence of a magnesium deficiency in 38 percent of a group of 1,300 patients.[52]

Although the literature is too sparse to draw firm conclusions, many CFS patients

Table 4: Magnesium Deficiency or CFS?

1. Neuromuscular and psychiatric disorders

   - Symptoms

chronic fatigue	depression
weakness	anxiety
paresthesias	sleep disturbances
myalgias	migraine & tension headaches

   - Objective Findings
     - EEG abnormalities
     - electromyographic abnormalities
     - sensorineural abnormalities

2. Immunologic disorders with an inappropriate response to viral infections including:
   - both higher and lower antibody responses.
   - depressed natural killer cell activity.
   - altered cytokine and interleukin release.
   - abnormal delayed skin sensitivity.
   - mild immune dysfunctions.
   - hypereosinophilia (only with myalgia).

3. Increase in substance P.*

4. Increase in NMDA (n-methyl-d-aspartate) receptor activity.**

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* Substance P is a neuropeptide isolated from brain tissues and the gastrointestinal tract. It promotes inflammation and inflammatory pain, bronchospasm, and capillary permeability. The result may be edema, chronic urticaria, rhinitis or any of several neuropsychiatric disorders.

** The NMDA receptor is part of the brain's neuroexcitatory pathway. Upregulation of the receptor is found in CFS and causes a variety of neuromuscular and psychiatric symptoms. It is also found in magnesium deficiency as magnesium inhibits the NMDA receptor.

who are magnesium-deficient could possibly derive benefit from magnesium supplementation. Perhaps the best clinical study to date involved patients with low erythrocyte magnesium levels who randomly received 100 mg magnesium IM or placebo each week for six weeks. Twelve of the 15 patients who received magnesium felt better compared to only three of the 17 patients who received placebo. Moreover, erythrocyte magnesium levels returned to normal in all of the patients receiving magnesium, but in only one patient who received placebo.[51] These findings are consistent with a report that CFS patients who were not magnesium-deficient failed to benefit from an injection of 580 mg magnesium, six times the

Table 5: Marginal Magnesium Deficiency in CFS

Investigators	# of Patients	Lab Measures	Magnesium
Grant et al (1996)	28	RBC	⇓ in 5/18 = 18% ⇓ ave. concentrations
Hinds et al (1994)	89 6	RBC loading test	similar to controls similar to controls
Clague (1994)	12	plasma, whole blood, RBC, loading test	similar to controls
Howard et al (1992)	several hundred	WBC, loading test, RBC (optional)	⇓ in at least 50%
Jessop (1992)	1324	loading test	⇓ in 38%
Doulofeu (1991)	18	serum, RBC, whole blood	similar to controls
Gantz (1991)	20	RBC	normal in 15; ⇑ concentrations in 5
Cox et al. (1991)	20	RBC	⇓ ave. concentrations

dosage received by the group of magnesium-deficient patients.[48]

Particularly when fibromyalgia is a substantial component of the clinical picture, magnesium supplementation has often been combined with malic acid, since malate plays an important role in energy metabolism; specifically the generation of mitochondrial ATP. Abraham and Flechas originally proposed using the combination and presented the results of an open trial in which primary fibromyalgia patients were treated for an average of eight weeks with 200-600 mg magnesium and 1,200-2,400 mg malate daily. The subjects exhibited a significant decrease in mean tender point index from 19.6 to 6.5. Two days after six of the 15 patients were switched to placebo, they reported muscle pain had worsened. After two weeks, their mean tender point index had risen from 6.8 to 21.5.[54]

While these results are promising, a subsequent double-blind crossover study of primary fibromyalgia patients who received 300 mg magnesium and 1200 mg malic acid or placebo in random order for four weeks, each with a two-week washout period in between, failed to find significant improvements in pain, tenderness, and functional or psychological measures.[55]

If this study were to be repeated using twice the dosage, lasting eight weeks, and including CFS patients, the results might be different. In the meantime, we have only the informal observations of some clinicians who find that, while pain from fibromyalgia appears to respond in about two days, fatigue may take two weeks to respond. According to one clinician, 40 percent of patients with CFS show improvement after starting supplementation.[56]

Sodium (neurally-mediated hypotension)

Neurally-mediated hypotension, a term that refers to an abnormal neurocardiogenic reflex in individuals with structurally normal hearts, is a common cause of recurrent lightheadedness and fainting. When venous pooling during long sitting or standing causes a reduced ventricular preload, susceptible people respond with an increased catecholamine response, resulting in augmented inotropic activity and excessive stimulation of mechanoreceptors in the left ventricle. This causes an exaggerated parasympathetic response, resulting in vasodilation, bradycardia, hypotension, and possibly syncope.[57] After the episode, fatigue is prominent and may last for an extensive period of time.[58]

Neurally-mediated hypotension has now been identified as a common finding in chronic fatigue syndrome. In one study, 23 CFS patients were tested on a table designed to tilt them upright at various angles. Twenty-two of the 23 patients showed evidence of neurally-mediated hypotension as compared to only four of 14 normal controls; moreover, nine of the patients reported complete or nearly complete resolution of CFS after this pathophysiological response was adequately treated.[59]

Of particular interest was the finding that nearly two-thirds of the CFS patients in this study reported they usually or always tried to avoid salt and salty foods. Symptoms associated with inadequate sodium intake include undue fatigue after moderate exertion, lassitude, headache, sleeplessness, and inability to concentrate;[60] this symptom complex has even been reproduced with experimental salt restriction.[61] The ability of sodium intake to affect blood pressure regulation through its effect on blood volume is well known, suggesting this subgroup of CFS patients may benefit by moderately increasing their salt intake.

Zinc

Zinc is another mineral often marginally deficient in CFS. In one study of 28 women, mean red-cell zinc concentrations, although within the normal range, were significantly lower than in a group of healthy controls.[25] A second informal, clinical study found that, of 1,300 CFS patients, nearly one-third had evidence of zinc deficiency as manifested by low blood-zinc concentrations or leukonychia.[52]

It is interesting that zinc deficiency can cause immunodepression[62] and produce muscle pain and fatigue.[63] While a marginal serum deficiency would be unlikely to reduce muscle zinc nutriture, changes in extracellular zinc levels have been reported to influence the twitch-tension relationship in muscle, presumably due to a direct effect at the level of the cellular membrane.[64]

Leukonychia, a term referring to white spots on the fingernails, is believed to be a sign of marginal zinc deficiency and has been found to be correlated with frequent feelings of drowsiness.[65] However, its prevalence in CFS is unknown. Also, erythrocyte zinc levels were found to be abnormally low in over half of a group of randomly selected patients who reported having chemical sensitivities,[68] suggesting that zinc deficiency may be more likely in CFS patients who are chemically sensitive.

Unfortunately, the results of zinc supplementation in CFS have yet to be reported, so its potential contribution to treatment can only be speculated. When normal volunteers with no evidence of zinc deficiency were supplemented with 135 mg of zinc daily for 15 days, they developed increased isokinetic strength and isometric endurance in their leg muscles.[63] If normals can improve muscle function with zinc supplementation, supplementing marginally zinc-deficient CFS patients may promote improvement in muscle physiology.

Other Nutritional Factors

L-Tryptophan

Two separate clinical notes have reported that L-tryptophan was depressed in the plasma of 80 percent of a group of CFS patients, a larger percentage than all other amino acids analyzed.[67,68] Fibromyalgia patients have similar findings. For example, in a study of patients with a severe level of pain, plasma free tryptophan levels were inversely related to pain severity.[69] Also, when fibromyalgia patients were compared to controls, plasma tryptophan levels tended to be lower in the patient group and their transport ratio of tryptophan to other competing amino acids was significantly decreased, suggesting that brain serotonin levels may be depressed.[70]

Tryptophan is the dietary precursor of serotonin, a neurotransmitter intimately connected with mood. For example, a low tryptophan diet may cause relapse in recovering depressives,[71] while low tryptophan concentrations may rise when depression remits.[72] However, the efficacy of tryptophan supplementation in treating fatigue and depression in CFS patients is unknown.

Tryptophan supplementation usually provides a mild degree of analgesia and may be especially effective for the subset of chronic pain patients with a disorder of serotonergic transmission.[73] While its efficacy in CFS has not been explored, there has been some interesting work reported in patients with fibromyalgia.

In one study of fibromyalgia patients with severe musculoskeletal pain, plasma free tryptophan levels were measured and found to be inversely related to the severity of subjective pain.[69] Evidence that tryptophan has a causal relationship to pain comes from an open trial involving 50 fibromyalgia patients. They received 100 mg three times daily of 5-hydroxytryptophan, a metabolite of tryptophan and immediate precursor of serotonin. After three months, half of the group had a fair-to-good degree of overall improvement, with highly significant improvements in fatigue, number of tender points, pain intensity, anxiety, and sleep quality.[74] These results were similar to those of an earlier double-blind study by the same group of investigators.[75]

There is enhanced degradation of tryptophan in infectious diseases, possibly due to the increased formation of gamma interferon during activation of cell-mediated immunity.[76] However, it is not known whether correcting a tryptophan deficiency will enhance cell-mediated immunity in virally-mediated illnesses.

L-Carnitine

Carnitine and its esters prevent toxic accumulations of fatty acids in the cellular cytoplasm, and of acyl CoA in the mitochondria, while providing acetyl CoA for mitochondrial energy production.

Because of its important role in muscle metabolism, carnitine deficiency may well impair mitochondrial function. If so, it could cause symptoms of generalized fatigue along with myalgia, muscle weakness, and malaise following physical exertion.[77]

The evidence to date suggests some CFS patients may suffer from a clinically-relevant carnitine deficiency. While findings concerning free serum carnitine levels have been mixed, studies have found significant decreases in serum acylcarnitine.[77-79] Moreover, a third study found an increased ratio of acylcarnitine to free carnitine,[25] a finding which suggests insufficient carnitine is available for metabolic requirements.[83]

Most importantly from a clinical perspective, one of these studies found both total and free serum carnitine levels were inversely correlated with patient symptoms, and serum carnitine levels were directly correlated with capacity to function.[79] Moreover, another of these studies found a similar relationship between serum acylcarnitine, symptoms, and functional capacity.[77] In other words, in CFS, serum carnitine levels appear to be a biochemical

marker for both symptom severity and ability to function.

Clinical trials of oral L-carnitine, using up to 1 gm three to four times daily, have shown mixed results.[79,80,82] Plioplys believes this is because only one-third of CFS patients are carnitine responders. Of the responders, some improve so dramatically that, even if they were fully disabled initially, they return to normal functioning and remain well if they continue taking the supplement. Unfortunately, he found baseline serum levels of L-carnitine failed to predict who would respond.[79,80]

Studies with AIDS patients suggest the possibility that another measure may better identify carnitine-responsive patients. Similar to CFS patients, AIDS patients tend to have low serum carnitine, although some have elevated levels. However, mononuclear carnitine levels are low in both the low- and high-carnitine subgroups.[83]

When a group of AIDS patients with low mononuclear carnitine took six grams L-carnitine daily, an improvement in metabolic and immunological parameters was noted, and the response occurred after only two weeks of supplementation.[83] CFS patients also have low mononuclear cell carnitine levels,[84] so possibly mononuclear cell carnitine will prove to be a better predictor of carnitine response. And, six grams daily may be a more effective dosage. Of course, because the metabolic and immunologic parameters in AIDS are quite different from those of CFS, it is premature to assume that what applies to one patient population will also apply to the other.

Coenzyme Q10

Since CoQ10 facilitates cellular respiration, and because clinicians believe it is of therapeutic value, it has long been prescribed to CFS patients.[85,86] Judy presented a formal study of 20 female patients who required bed rest following mild exercise. They were compared to 20 sedentary sex-, age-, and weight-matched normal controls. Eighty percent were deficient in CoQ10, which further decreased following mild exercise or over the course of normal daytime activity. Three months following supplementation with 100 mg CoQ10 daily, exercise tolerance (400 kg-meters of work) more than doubled; all patients had improved. Ninety percent had reduction and/or disappearance of clinical symptoms, and 85 percent had decreased post-exercise fatigue.[87]

Essential Fatty Acids

Low levels of essential fatty acids (EFAs) appear to be a common finding in chronic fatigue syndrome.[26,88] It has been theorized this finding is due to abnormalities in EFA metabolism. Gray and Martinovic found changes in the ratio of biologically active EFA metabolites such as would be expected as an exaggeration of normal physiological response to excessive or prolonged stress. They postulated these changes in EFA metabolites, in turn, could cause the immune, endocrine, and sympathetic nervous system dysfunctions seen in CFS.[89]

Horrobin has noted that viruses, as part of their attack strategy, may reduce the ability of cells to make 6-desaturated EFAs while interferon requires 6-desaturated EFAs in order to exert its antiviral effects.[90] In addition, it is quite possible that supplementation with essential fatty acids may improve the hemorrheological abnormalities found in CFS alluded to earlier. The formation of prostaglandin E_1, for example, can be enhanced by increasing intake of omega-6 fatty acids. This prostaglandin has been shown to improve erythrocyte membrane fluidity[91] and filterability;[92] i.e., the ability of erythrocytes to pass through a small membrane filter. Moreover, supplementation with both evening primrose oil, a source of omega-6 fatty acids,[93] and fish oils,[94] a source of omega-3 fatty acids, has been shown to improve erythrocyte filterability.

Early research suggests EFA supplementation may be effective for the treatment of CFS. The best study to date concerned a

Table 6: Nutritional Supplementation for CFS

Nutrient	Tentative Protocol	Possible Benefits
Folic Acid	1 - 10 mg/d for 3 mo. trial	⇓ fatigue & depression; improved immune function
Vitamin B12	total of 6,000 -70,000 μg IM/ wk for 3 wk. trial	⇓ fatigue, depression and pain; improved microcirculation
Vitamin C	10 - 15 g daily	improved immune function; ⇓ pain; improved microcirculation
Magnesium	if ⇓ RBC Mg: 100 mg IM/wk x 6 wks. - and Malic Acid Mg: 600 mg/d; Malic Acid 2400 mg/d (8 week trial)	subjective improvement ⇓ muscle pain
Sodium	if Dx of neurally-mediated hypotension: ⇑ sodium intake moderately	subjective improvement
Zinc	135 mg/d x 15 days	⇑ muscle strength & endurance; ⇓ pain & fatigue improved immune function
L-Tryptophan	in fibromyalgia: 5-hydroxytryptophan 100 mg 3 times daily (3 month trial)	⇓ pain & fatigue
L-Carnitine	1-2 g 3 times daily (3 month trial)	improvement that can be dramatic
Coenzyme Q10	100 mg daily (3 month trial)	marked improvement with ⇑ muscle endurance
Essential Fatty Acids	280 mg GLA & 135 mg EPA daily (3 month trial)	general improvement

group of 63 patients with a good employment and mental health history who had post-viral fatigue syndrome for at least one year. As expected, their baseline plasma EFA levels were found to be low. They randomly received four capsules twice daily of either an olive oil placebo or a mixture of 80-percent evening primrose oil and 20-percent concentrated fish oil (35 mg GLA and 17 mg EPA per capsule). After three months, 85 percent of treated patients rated themselves as better than at baseline compared to 17 percent of those on placebo, a highly significant difference. Without exception, the individual symptoms, including fatigue, aches and pains, and depression, showed a significantly greater improvement on the fatty acid supplement than on placebo. Moreover, in the treated group only, plasma EFA levels rose to normal and monounsaturated and saturated fatty acid levels, which had been elevated, normalized.[91]

A recent attempt to replicate these results was unsuccessful.[95] However, there were positive findings in an open trial of a group of 29 CFS patients who had been ill for an average of 5.9 years. They received essential fatty acid supplements along with psychological help and graded exercise. Only two of these patients showed any improvement in the 12 months prior to starting the program, while 27 of them significantly improved within the program's first three months. Twenty-eight of the 29 patients were followed-up an average of 16 months later. All but one of them were still improved compared to before treatment, and 20 of 28 had made further progress.[89]

Overview and Recommendations

Any of the nutrients discussed above could be marginally deficient in CFS patients, a finding that appears to be primarily due to the illness process rather than to inadequate diets. In one study, for example, CFS patients had a similar dietary quality to that of healthy volunteers. Moreover, they reported the use of vitamin/mineral supplements containing 100-200 percent of the RDA significantly more frequently, and their intake of iron, magnesium, and zinc was greater.[25]

It is likely that marginal deficiencies not only contribute to the clinical manifestations of chronic fatigue syndrome, but also are detrimental to the healing processes. Therefore, when feasible, they should be identified by objective testing and their resolution should be assured by repeat testing following the initiation of treatment.

Moreover, because of the rarity of serious adverse reactions and the difficulty in ruling out marginal deficiencies, and because some of the therapeutic benefits of nutritional supplements appear to be due to pharmacological effects, it seems rational to consider supplementing CFS patients with the nutrients discussed above, along with a general high-potency vitamin/mineral supplement, at least for a trial period. See Table 6.

The need for more research in this area is obvious; in the meantime, it will be necessary to rely on the present data, along with a hefty dose of clinical experience to formulate the best possible program of therapeutic nutrition for these patients.

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