FRANKLIN CARDIOVASCULAR ASSOCIATES, PA

Autonomic dysfunction disorders
High risk primary and secondary prevention of cardiovascular disorders and complicated dyslipidemia specialization

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RE: Article on Chronic Fatigue

TITLE OF ARTICLE: Myalgic Encephalomyelitis (ME) / Chronic Fatigue Syndrome (CFS).

INTRODUCTION:

Chronic fatigue syndrome (CFS) is also called myalgic encephalomyelitis (ME). It is a challenge to physicians both to diagnosis and treat. It is believed the prevalence is approximately 1% in the general population.

The cause of ME/CFS is unknown. Its mechanism of causing disease is also unknown. It is actually an independent unique disease. No two patients have the same type of symptoms and the associated circumstances vary among individuals. In addition, there was no consistent diagnostic criteria. Over the last 30 years, diagnostic criteria have continuously changed. This is because, as mentioned, there are no unique features of the disease that make for a set pattern.

There is a wide range of differential diagnostic possibilities in individuals who have a chronic-fatigue-type presentation. They may be somatic or psychiatric (psychiatric/psychosomatic). Differential diagnoses include chronic infections, neurodegenerative diseases such as multiple sclerosis, endocrine diseases such as thyroid insufficiency and adrenal insufficiency, collagen vascular diseases such as lupus and rheumatoid arthritis, muscles diseases such as myositis, various blood disorders with anemia components, cardiomyopathies, coronary artery disease, obstructive sleep apnea and various metabolic abnormalities. Oftentimes, various tests have to be performed to exclude these entities before one can make a presumptive diagnosis of ME/CFS.

Realizing that this is a unique constellation of symptoms and disease presentation, it is difficult to have a standard definition, generally accepted that symptoms of fatigue and tiredness should be occurring for at least six months. Also, that half of the time they should be of moderate to severe intensity. One of the hallmarks is postexertional malaise. Unrefreshing sleep and an altered sleep pattern is also noted.

Patients often have cognitive impairment, which is worsened by exertion or stress. Also, one may exhibit difficulties with memory and thinking clearly. A major symptom is one that is known as

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orthostatic intolerance, that is when one is standing, they have an increase in symptoms of fatigue, brain fog and

dizziness. It is believed that lack of blood flow to the brain, that is cerebral hypoperfusion, is an operative mechanism in this symptom complex. Some patients with ME/CFS also have GI symptoms such as irritable bowel syndrome and also headache symptoms.

It is estimated that up to 2.5 million people in the United States may be affected with this disorder. No infectious agents have been proven to cause the syndrome.

The classical prototype patient is one who has a sudden onset of symptoms after being highly functioning. Individuals are afflicted in the prime of their life suddenly with multiple somatic complaints. They were extremely functional, in that many times industrious prior to the sudden onset of these symptoms of chronic fatigue. Most often, these patients do not have somatic complaints such as back pain and headaches prior to the emergence of the disorder. Painful lymph notes, but not lymphadenopathy is often present in individuals. There is some overlap and confusion between the ME/CFS syndrome complex and the entity known as fibromyalgia. Both entities can have trigger points which elicit pain. Fibromyalgia is a disorder of chronic pain and sleep disorder and oftentimes associated with a chronic fatigue presentation. We believe that chronic fatigue and fibromyalgia-type symptoms are part of a spectrum of disorders which are caused by orthostatic intolerance and abnormal autonomic function, where there is a lack of cerebral blood flow to the brain when one assumes the upright position.

ME/CFS often starts after or during an infection. It is believed that many patients have a genetic predisposition to this. Some have postulated that there is a generation of B lymphocytes that are cloned and prone to autoreactivity. Others believe that there is a T-cell-mediated mechanism. ME/CFS is considered by many a neuromuscular disease with postexertional malaise. The incidence between females and males is 2:1. by our experience it's higher. An interesting theory that chronic fatigue syndrome may be based on autonomic dysfunction, or neurally mediated hypotension was supported by a study involving a tilt test.

In one study, 23 patients with ME/CFS had tilt tests and 22 had an abnormal test compared to 4/14 unmatched controls. This small pilot study showed that Florinef, which is a mineralocorticoid that retains salt water and atenolol, which is a beta-blocker and disopyramide, which has anticholinergic

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mechanisms improve patients. A larger study of 600 patients with CFS, showed that 77% had abnormal tilt, not quite as high as the small pilot study.

We have used various HRV testing modalities which also show dynamic stand abnormalities. We have found that a tilt test, which reproduces many symptoms and may show autonomic system abnormalities is neither a sensitive or specific test in general for detection in many autonomic abnormalities. We have used office-based heart rate variability tests sometimes with limited tilts of five minutes, instead of prolonged tilts of 40 minutes to better assess abnormalities in the autonomic system. Also, testing sweat gland function with sudomotor testing can determine if there are abnormalities in small fibers which are the transmitting autonomic nerves.

Perhaps the common pathway with ME/CFS involves inflammation and oxidative stress. Studies have shown that there is a shared inflammatory and oxidative and nitrosative pathway. What happens is there is oxidative damage to DNA molecules, and this can cause damage to subcellular particles such as mitochondria. Oxidative damage is also a risk factor for atherosclerosis and neurodegeneration and therefore this may explain increased cardiovascular morbidity and mortality, which can potentially occur with chronic fatigue syndrome, as all of these processes involve oxidative damage to DNA. Studies measuring urinary excretion of (8-hydroxy deoxyguanosine (8-OHdG) have shown that individuals with ME/CFS have much higher levels in the urine than controls. Basically, any viral or bacterial infection can precipitate a cascade of oxidative damage and lead to ME/CFS. Epstein-Barr virus originally postulated as one of the culprits has been found not to be uniquely associated with this disease entity. While mononucleosis can cause prolonged significant fatigue status post an episode, many times this resolves in patients and many patients develop ME/CFS without having a mononucleosis-like syndrome preceding.

Plasma coenzyme Q10 levels have also been found to be lower in patients with ME/CFS as they are also lower in treatment of resistant depression. There is overlap between resistant depression and chronic fatigue syndrome in many respects including lower levels of coenzyme Q10 and oxidative stress pathways, which have been identified.

Other studies have shown decrease in omega-3 and polyunsaturated fatty acids in people with ME/CFS, the so called PUFA levels. There is also an increase in omega-6 PUFA and saturated fats in individuals with ME/CFS.

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Studies have shown that chronic fatigue syndrome increases autoimmune activation against 5-HT involving serotonin pathways. Also, there are higher TNF alpha levels, IL-1 and IL-6 levels and increased IgA response against lipoproteins of commensal bacteria, the so called "gut leak phenomena." Elastase

levels are also noted to be elevated in patients with CFS compared to healthy controls. This has led to the hypothesis that ME/CFS is a neuroimmune disease. There is data that also suggests that it may not just be a B-cell but may be T-cell mediated immunity response evidenced by the fact that there are increased neopterin levels.

While no molecular mechanisms have been found to be unique in chronic fatigue syndrome and various viral agents are believed to set off a cascade of oxidative stress to cause this syndrome, studies have shown that mitochondrial dysfunction has been found in ME/CFS. These studies have shown lower ATP, the energy molecule of the body, production. These have also shown impaired oxidative phosphorylation and damage to the mitochondria. As mentioned, there are increased cytokines such as IL-1, TNA alpha, and elastase, which inhibit mitochondrial respiration and decreased activity of the electron transport chain where ATP molecules are produced within the cell. These inflammatory cytokines also increase mitochondrial membrane permeability causing mitochondrial to shut down. It may be that the decrease in ATP production causes chronic fatigue symptoms, post-exertional malaise, impaired glucose utilization and glucose hypometabolism and cerebral hypoperfusion, the latter of which is extremely important in orthostatic intolerance syndromes.

Since we believe that chronic fatigue syndrome is an acquired mitochondrial dysfunction due to an inciting agent, whether it be a virus, bacterial infection, chronic stress, concussion trauma, etc., it is important to understand that mitochondria are extremely plentiful in neurons and that the autonomic nervous system neurons are most susceptible to damage. Therefore, the majority of patients we have found with chronic fatigue syndrome have orthostatic intolerance and cannot stand for prolonged periods of time, are tired with minimal activity and have to lie down often and have no energy. It is believed that efficiency of ATP from damaged mitochondria may be the common pathway after oxidative stress has occurred. We have found that venous pooling in the legs on standing is oftentimes a common feature of many patients with chronic fatigue syndrome. This can be assessed with HRV-type office devices and one can follow the progression or improvement in chronic fatigue syndrome with treatment by monitoring changes both in patient symptoms, exercise tolerance and degree of what we call “sympathetic withdraw”, or venous pooling in the legs.

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Treatment is difficult. Antivirals have been disappointing. Antibiotics have shown no significant response. Immunomodulating agents are experimental and there is no definitive data on these at the present time. Glucocorticoids have shown positive results in some studies but do cause adrenal

insufficiency. Florinef, a more mineralocorticoid which retains salt and water in the body, has been helpful in a significant amount of people, but only gives a partial response, and in higher doses gives side-effects also such as low potassium and edema of the legs and headaches. Oftentimes, we will use Florinef at very low doses with Midodrine at low doses. Using low doses of two agents, Florinef, a mineralocorticoid and Midodrine, an alpha agonist, which constricts the veins and arteries and promotes blood flow to go vertically to the head, are often effective with low adverse effects. This is amplified with use of compression stocking and salt water intake. Graded exercise programs have been useful, especially when starting out with supine exercises with swimming or rowing machines and gradually graduating to elliptical machines and eventually treadmill, or other vertical aerobic exercises. Nortriptyline has helped sleep and we have found it to be extremely helpful in chronic fatigue syndromes to improve the disturbed sleep and disturbances that are present. Also, when there appears to be a high vagal dominant state in these patients, the anticholinergic effects of very low dose nortriptyline are helpful. We use nortriptyline in low doses of 10 mg a day to act more as an anticholinergic and not as an antidepressant. Cognitive behavior therapy has also been shown to be helpful. Individuals have used stimulants such as modafinil, which has shown poor results. Methylphenidate has been shown to decrease fatigue and increases concentration in people with chronic fatigue syndromes. However, many individuals with these disorders have orthostatic intolerance and rapid heart rates and these are worsened. In addition, the cardiac adverse effects of these types of medications preclude their long-term use in our opinion. We have found that especially in patients with orthostatic intolerance syndromes such as postural orthostatic tachycardia, or POTS, their symptoms may actually worsen with increased tachycardia and heart rates.

Our approach to treating ME/CFS involves testing for autonomic dysfunction. Once we have identified some abnormalities in the autonomic nervous system, which are present in a large number of patients (up to 97% of patients had abnormal tilt tests in one study), we prescribed therapy directed at improving the dysautonomic function. Compression garments and compression stockings, fluids of up to 64 ounces a day, liberal salt intake and counter maneuvers to increase venous return to the heart and brain are often helpful but are only palliative. Elevating the head of the bed during sleep prevents Pharmacology using agents such as Midodrine and Florinef in the appropriate doses are oftentimes very helpful in patients who show evidence of orthostatic intolerance on testing or with symptoms. Other more advanced medications can be used if individuals are refractory to these initial stages.

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Mitochondrial antioxidant cocktails involving alpha lipoic acid, L-carnitine and coenzyme Q10 we have found to be very helpful, and there is preliminary data showing that alpha lipoic acid especially is helpful in treating the small fiber disease associated with autonomic dysfunction. It is a very potent antioxidant

that recycles natural antioxidants in the body. We have also found chronic fatigue to be significantly benefited by nitric oxide production using beet root extracts, which use salivary gland enzymes to manufacture nitric oxide. In patients over the age of 40, we have also used L-arginine and L-citrulline which go through a different nitric oxide production pathway, the nitric oxide synthase pathway. Omega-3 supplementation, which is anti-inflammatory, is also helpful as is a Mediterranean diet, which incorporates fish and other omega-3 products. Stress reduction and of course graduated exercise are also important components. A proper diet is extremely effective especially one that increases omega-3 levels. A diet that is anti-inflammatory such as a Mediterranean diet, is also a significant benefit. Drinking rapidly a small bottle of plain water on awakening before even getting up out of bed activated the sympathetic nervous system and is useful to start the day as mornings are usually very tough times on patients.

Diagnosis and treatment of ME/CFS requires a coordinated team effort on the part of the patient, physician, ancillary staff and oftentimes a dietician and exercise physiologist. Many individuals do improve with a holistic treatment approach and are able to function again, whereas they were incapable of gainful employment and nonfunctioning at their initial presentation. We have seen individuals present to us with cold extremities of the hands and feet, brain fog, inability to concentrate, word-finding difficulties and severe fatigue after minimal activity in time respond with a multifactorial treatment approach.

While the common denominator of what causes chronic fatigue syndrome is still under investigation, we strongly believe that it begins at the cellular level where oxidative stress damages mitochondria and ATP production, which is the energy molecule of the body, is produced in low quantities and therefore mitochondrial antioxidant cocktails are an intricate part of treatment. However, physically and pharmacologically promoting blood flow from the lower extremity to the head is most important initially, as individuals have signs and symptoms of cerebral and peripheral hypoperfusion which requires fluid resuscitation, salt, ancillary physical support mechanisms including compression stockings and targeted pharmacology.

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Sincerely,

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