Antiviral Intervention for Chronic Fatigue Syndrome

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Chronic Fatigue Syndrome (CFS) has a long history in medical literature. In the past it has been referred to as chronic Epstein-Barr virus syndrome (EBV), chronic mononucleosis syndrome, postviral fatigue syndrome, epidemic myalgic encephalomyelitis and even "yuppie flu." In 1994 the Center for Disease Control refined the definition of CFS.

CDC, NIH and International Chronic Fatigue Syndrome Study Group Criteria for Diagnosis of Chronic Fatigue Syndrome

A case of CFS must fulfill all major criteria, plus four or more of the minor criteria. Each minor criterion must have persisted or recurred during six or more consecutive months of illness and must not have predated the fatigue. A patient who does not fully meet the CFS criteria may be given a diagnosis of idiopathic chronic fatigue.

Major Criteria

- Unexplained, persistent or relapsing fatigue that is new or definite onset (not lifelong)
- Fatigue is not due to ongoing exertion
- Fatigue is not substantially alleviated by rest
- Fatigue easily results in substantial reduction in previous levels of occupational, educational, social, or personal activities

Minor Criteria

1. 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.
2. Sore throat
3. Tender cervical or axillary lymph nodes
4. Muscle pain
5. Multijoint pain without swelling or redness
6. Headaches of a new type, pattern or severity
7. Unrefreshing sleep
8. Postexertional malaise lasting more than 24 hours.

It has been observed that CFS occurs after a viral illness such as a severe flu. Many patients describe a relapse of an illness after which CFS occurs because more rest and a longer period of convalescence were required to recover. Initial symptoms of CFS are viral and include swollen glands, sore throat, fatigue, malaise and fever. A host of viruses has been associated with CFS including influenza, EBV, cytomegalovirus, coxsackie, polio, human herpes virus 6 (HHV-6), enteroviruses, herpes simplex 1 & 2, human T-cell lymphotropic viruses, and retrovirus. It is possible that prions and stealth viruses yet to be identified may also be involved in this illness and many may be co-infected with more than one virus. Numerous immune abnormalities have been seen in patients with CFS including decreased natural killer cell (NK) function, alterations in interferons (INF), interleukins and other cytokines and tumor necrosis factor (TNF).

To date there are no safe and effective antiviral drugs to treat CFS. However, there are many natural compounds that are safe and effective and have broad antiviral action, many of which also modulate immune function to fight viruses. Additionally, some of these compounds have the added benefit of antifungal and antibacterial activity. Chronic immune suppression often results in candidiasis (Candida albicans infection) which can cause further immunosuppression.

Glycyrrhizin

Glycyrrhizin (GL) is one of the active antiviral compounds found in licorice root (Glyrrhiza glabra). It has been used in Japan as an intravenous drug for more than 20 years as Stronger Neo-Minophagen C (SNMC) and research has shown it to be extremely effective for hepatitis (A, B, C), HIV, cancer and many other serious viral illnesses. Licorice is in many Kampo medicines (Japanese Herbal Medicine) for immune modulation and antiviral therapy. GL is absorbed orally. GL is a conjugate of glycyrrhetinic acid (GA) and glucuronic acid. Oral GL is metabolized in the intestine to GA and both are active antiviral compounds. Intravenous GL is metabolized into GA when excreted through the bile into the intestines. GL and GA exhibit similar properties. Both have been shown to be effective for hepatitis A, B, C; Human Immunodeficiency virus (HIV); Herpes (I, II, Zoster, perhaps HHV- 6); lichen planus, influenza, cytomegalovirus (CMV), cancer, phlebovirus and vaccinia virus. GL/GA increases the effectiveness of INF therapy in patients with hepatitis C. GL/GA also modulates cortisol levels which are often abnormal in patients with CFS. These compounds improve immunocompetence and reduce susceptibility to candida albicans. GL/GA are antibacterial to *H. pylori* and *klebsiella pneumoniae*.

GL/GA have direct antiviral activity and can inhibit some RNA transcriptases (HIV). They also have an indirect antiviral action and can decrease cell membrane permeability (e.g. decrease hepatocyte injury in hepatitis); inactivate viruses and inhibit viral proliferation. Both compounds are also potent antioxidants and free radical scavengers and protect normal, healthy cells from injury. GL/GA can increase gamma interferon, T cells, NK cells and improve immune function. They also selectively inhibit cytolytic reactivity of the complement system. However, these compounds do not inhibit (may enhance) immune adherence responsible for immune phagocytosis, regulation of antibody

production in protective immunity against invaders. GL/GA also inhibits the arachidonic acid cascade (phospholipase A2) thereby reducing inflammation.

SNMC 20 ml ampoules for IV use provide 40 mg GL, 400 mg glycine, and 20 mg L-cysteine. The therapeutic IV dose range for SNMC is from 40 to 60 ml and may go as high as 100 ml for a therapeutic effect. Oral intake of GL and/or GA ranges from 150-300 mg/day. SNMC has aminoacetic acid and L-cysteine added to prevent pseudo-aldosteronism resulting in sodium retention, potassium depletion and hypertension. Pseudo-aldosteronism is rarely reported at therapeutic doses but can be treated with spironolactone and perhaps prevented with potassium supplementation and consuming potassium rich foods. Patients taking GL or GA should routinely monitor their blood pressure. However, hypertension has not generally been observed in patients with CFS (clinical observation). CFS patients often have postural hypotension and perhaps they are not susceptible to this adverse effect.

Lauric Acid/Monolaurin

Lauric acid was first discovered as the main antiviral and antibacterial substance in human breast milk. It is a medium chain, saturated fatty acid that is also found in coconut products. Monolaurin is the glycerol ester of lauric acid and is more biologically active than lauric acid. Monolaurin has been shown to be active against influenza virus, pneumovirus, paramyxovirus (Newcastle), morbillivirus (rubeola), coronavirus (avian infectious, bronchitis virus), herpes simplex I & II, CMV, EBV, and HIV. Monolaurin disrupts the lipid bilayer of the virus preventing attachment to susceptible host cells. It binds to the lipid-protein envelope of the virus and inactivates the virus. Monolaurin inhibits the replication of viruses by interrupting the binding of virus to host cells and prevents uncoating of viruses necessary for replication and infection. Monolaurin can remove all measurable infectivity by directly disintegrating the viral envelope. Monolaurin binding to the viral envelope makes a virus more susceptible to host defenses.

Monolaurin is effective against yeast and fungi, *staphylococcus aureus* and *streptococcus agalactiae, chlamydia trachomatis, candida albicans, giardia lamblia*, ringworm, *H. pylori* and gonorrhea. Monolaurin is non-toxic and listed in GRAS (Generally Recognized as Safe) as a food emulsifier. A therapeutic dose of monolaurin is generally 1800 mg to 2400 mg per day.

Quercetin

Quercetin is a flavonoid compound that is found in many foods including apples, onions, medicinal herbs and tea. Quercetin has been shown to be active against many types of cancer including: breast, prostate, colon, gastric, head and neck, leukemia, lung melanoma, liver, ovarian, cervical, rhabdomyosarcoma and it damages *cancer cells only*. In addition to its powerful antioxidant activity it is a potent aromatase inhibitor. Quercetin inhibits production of estrogen from DHEA and testosterone and also inhibits estrone sulfatase in the liver. It has anti-inflammatory effects and could help the muscle and joint pain associated with CFS. It also has strong anti-histamine activity and could improve the environmental and chemical sensitivities associated with CFS. It is immunostimulatory and antiviral against CMV, EBV, HIV, poliomyelitis and herpes simplex I & II. It blocks RNA transcriptase, impedes viral replication and increases reduced intracellular glutathione. Quercetin is non-toxic and the major flavonoid found in the US diet. It is estimated that Americans can consume approximately 25 mg/day. The therapeutic dose ranges from 2000 to 4000 mg/day.

N-Acetylcysteine

N-acetylcysteine (NAC) is a major antioxidant involved in liver detoxification and it is the precursor for glutathione. NAC is used to rescue patients from acetaminophen (Tylenol) liver damage and damage from other toxic chemicals. NAC is important for patients with chemical and environmental sensitivity. It is mucolytic and can improve mucous buildup in the lung and improve asthma. It is used as a prescription drug for oral and nasal application. NAC increases influenza virus specific lymphocyte proliferation, INF-gamma production and cytotoxic T-lymphocyte production to augment immune function. It has been shown to control EBV infection by reducing its replication and spread. NAC may block certain receptors interacting with viruses. Most of the antiviral work has focused on NAC's potent anti-HIV activity. Its antiviral activity against HIV is more potent when combined with vitamin C and glutathione (GSH). NAC increases the immunological function of NK and T cells in HIV infected patients. Depletion of NAC has adverse effects on macrophage and phagocyte function. NAC raises intracellular glutathione levels which is important for cell integrity. GSH and NAC may prevent/repair neuronal cell death by viruses such as HIV. NAC may be important to prevent and treat the memory and concentration impairments associated with CFS. Therapeutic doses range from 2000-4000 mg of NAC/day. Some practitioners add 1000-2000 mg of GSH since NAC and GSH together have a greater antiviral effect.

Coenzyme Q10

CoQ10 acts as a catalyst in the chain of chemical reactions that creates adenosine triphosphate (ATP) that is required as energy for every cell to function (aerobic metabolism). Viruses, cancer, CFIDS, and other disorders switch ATP production to anaerobic metabolism yielding less

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ATP and higher levels of lactic acid which induces muscle aches and fatigue. It is estimated that at least 80% of CFS patients are deficient in CoQ10. Compared to normal sedentary adults, CoQ10 significantly decreases even after mild exercise in patients with CFS. Unlike normal controls, these levels are not restored overnight. CoQ10 supplementation (100 mg/day) for three months in patients with CFS resulted in 100% improvement in exercise tolerance, 85% improvement in post-exercise fatigue and 90% improvement in overall symptoms. While most of the research on CoQ10 has focused on cardiovascular disease there are some reports suggesting it has some antiviral properties as well. Viral myocarditis caused by coxsackie virus was treated in mice either with Astragalus membranaceus (AM) plus taurine or CoQ10 given alone. Another group received all supplements together. Only AM with taurine *and* CoQ10 significantly reduced the mortality of the mice. All supplements could lighten myocardial histopathologic changes but results were greater when all supplements were given together. These results suggest some antiviral activity of CoQ10.

Exercise

Chronically ill patients have high levels of lactic acid due to a switch from predominantly aerobic to anaerobic glycolysis. Those with CFS experience symptoms of high levels of lactic acid such as fatigue, soreness and malaise which resemble overtraining symptoms. In order to have exercise recovery and lower lactic acid levels one must do aerobic exercise. The best way to initiate this exercise is to start with 3-5 minutes every other day and add 1-2 minutes each week until 30 minutes is sustained without stopping. Brisk walking outside or on a treadmill and cycling on a stationary bicycle or biking outside are examples of aerobic activities. After the patient is aerobically fit, they can either add more time (45-60 minutes) or they may do this 5 times per week if desired. They may also add strength training twice weekly on alternate days with weights or exercise bands (light to moderate intensity). It is very important that these patients do not overtrain.

Summary

An antiviral program should be taken with a broad spectrum multivitamin, multi-mineral supplement and anti-oxidants in divided doses throughout the day, rather than one large dose at once to make sure nutrient needs are being met. Antiviral compounds include GA and GL, monolaurin, quercetin, NAC, GSH and perhaps CoQ10. All of these substances have powerful antioxidant and anti-inflammatory activity as well. Many of these substances improve immune function and have anti-fungal and antibiotic activity. Other anti-inflammatory agents include fish oil, bromelain, curcumin, proanthocyanidins, ginger, high dose antioxidants and Ginkgo biloba. Ginkgo can also improve cognitive function as well. CoQ10 is important as it significantly improves post-exercise fatigue and overall symptoms. Incorporating aerobic exercise into the program is important as it reduces lactic acid, improves energy and reduces fatigue. Strength training should be added after the patient is aerobically fit to improve conditioning.

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