Treatment of CFS patients with elevated C4a using low dose erythropoietin corrects abnormalities in central nervous system metabolites and restores executive cognitive functioning.

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Objectives: Recent literature has supported the concept that erythropoietin (epo) is a neuroprotective agent for peripheral and central nervous system (CNS) that specifically prevents apoptosis of glial cells and improves capillary hypoperfusion in CNS. Treatment of patients with Chronic Fatigue Syndrome (CFS) and elevated levels of the anaphylatoxin C4a, an inflammatory product of activation of the complement cascade, using epo lowers C4a and reduces neurocognitive symptoms. Magnetic resonance spectroscopy (MRS) can demonstrate levels of metabolites that are markers for CNS function. A prospective clinical trial was performed to assess (1) safety of epo in CFS patients and those with elevated C4a; (2) efficacy of epo to improve symptoms, reduce C4a and correct abnormalities in CNS metabolites; (3) provide data that supports a testable hypothesis of the inflammatory origin of systemic and CNS symptoms in CFS.

Methods: 35 patients with CFS provided informed consent for an IRB-approved study. Symptoms of executive cognitive function, C4a and MRS of 1 cubic cm areas of left and right frontal lobes and left and right hippocampus before and after treatment with 5 doses of 8000 units of epo given by the study physician over 2 weeks were compared to known controls. Symptoms were recorded at each visit, as were levels of C4a and a review of possible adverse effects.

Results: Symptoms of executive cognitive function were reduced in cases after treatment, though still higher than in controls. C4a was reduced beginning after the second dose of epo, achieving values equal to controls in 91% of cases. MRS-determined values of n-acetyl acetate; creatine; choline did not change in cases and equaled controls. Myoinositol was elevated in 20% of cases with reduction after epo in all to control values. Lactate was elevated in 77%, with reduction in all after epo to controls. Ratios of glutamate to glutamine were abnormal in 97% of cases, with reduction to controls achieved in 55%. No adverse effects of clotting, elevation of blood pressure of development of iron deficiency anemia occurred.

Conclusions: Use of low dose epo in CFS patients is safe and effective to improve symptoms, C4a and CNS markers of abnormal glial cell function (myoinositol); capillary hypoperfusion (lactate); and excitatory neurotransmission (glutamate/glutamine). These results suggest that the systemic inflammation in CFS caused by elevated C4a may be treated using epo and that the CNS correlates of cognitive dysfunction in CFS patients has an inflammatory basis. A double blinded, placebo controlled trial is planned.