Current Shoemaker Biotoxin Research

We encourage you to visit www.biotoxin.info and learn about Dr. Ritchie Shoemaker, his protocols and his research. Many of our site visitors and contacts have been very pleased with the results of Dr. Shoemaker's protocols for damp building and mold-related illness. Some of the links below are on Dr. Shoemaker's site (for full articles, etc.), go to www.biotoxin.info and register to view these, first. (SMH)

http://www.biotoxin.info/current_research

Current Research

To be able to access full versions of Dr. Shoemaker's peer-reviewed articles you must be logged-in (on his above website) and will then see a menu option of "Published Shoemaker Research" under the "Research' menu.

National Toxicolgy Program Study Plan for Mold Research 2008

List of NTR Research Projects

Description of Research Needs

ASTMH Conference Presentation Abstract: Sequential upregulation of innate immune responses during acute acquisition of illness in patients exposed prospectively to water-damaged buildings (WDB)

Previous data demonstrated a pattern of innate immune inflammatory responses following re-exposure of patients made ill previously by exposure to a given WDB with evidence of amplified growth or toxigenic organisms, including fungi. This report expands those observations, using a prospective model that confirms causation of illness by exposure marked by upregulation of innate response elements measured daily following re-exposure including complement activation product C4a, leptin, MMP9, vascular endothelial growth factor (VEGF) and coagulation factors.

Following consent, 60 patients known to have a chronic biotoxin illness caused by exposure to a WDB followed a five step process: assessments of (i) symptoms (ii) VCS (iii) C4a (iv) leptin (v) MMP9 (vi) VEGF (vii) Factor VIII (viii) vWF (ix) vWF Ag were carried out at (1) baseline; (2) after first therapy with cholestyramine (CSM) (3) off CSM, without re-exposure for three days (4) after each of three days following re-exposure to suspected WDB (5) after second CSM treatment. Results were compared to known controls.

In patients (N=38) with illness recrudescence, upregulation of innate immune elements was observed: C4a increased after 24 hours; leptin increased after 24 hours; MMP9 increased after 48 hours; VEGF initially increased after 24 hours, falling after 72 hours. Factor VIII fell concomitantly with the rise in C4a; vWF fell after 72 hours. Episodes of epistaxis or hemoptysis were observed in 6 patients, coinciding with fall of vWF. Symptoms and VCS decline increased daily during re-exposure, reaching baseline levels after three days. Patients (N=22) without recrudescence showed no changes and equaled controls. Buildings with repeat illness patients continued to have evidence of ongoing water intrusion; sites without reacquisition had no evidence of ongoing water intrusion.

Re-exposure to WDB causes illness that can be identified by sequential changes in symptoms, VCS and innate immune responses. Use of sequential observation of symptoms, visual contrast sensitivity (VCS) and inflammatory responses following re-exposure to WDB can not only supports a model of disease mechanisms but can rapidly determine safety for re-occupancy.

Complement Split Products C3a and C4a Are Early Markers of Acute Lyme Disease in Tick-Bite Patients in the United States (Paper Accepted 2007 for publication in The International Archives of Allergy and Immunology)

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Abstract:

Background: Current laboratory markers do not readily detect acute Lyme disease. We assessed the utility of complement and its split products as markers of Lyme disease in patients shortly after a tick bite.

Methods: Thirty-one consecutive acute Lyme disease patients, 14 with and 17 without an erythema migrans (EM) skin rash, seen by a physician within 96 hours of a tick bite were matched with 24 consecutive tick-bite patients without Lyme disease symptoms and 46 healthy control subjects. Complement and split products measured included Factor B, Bb, C4, C3c, C3ades Arg, C4ades Arg, C1q- and C3d-containing immune complexes, and C2.

Results: C2, C4, C3, and Factor B levels were within normal ranges in all groups. C3a and C4a levels were significantly higher in acute Lyme disease patients than in tick-bite and healthy control groups (both $p<0.001$). All acute Lyme disease patients, regardless of EM, had elevated levels of C3a or C4a. Few tick-bite controls had elevated levels of C3a (2/20) or C4a (5/24); only one of the healthy control subjects had elevated C3a (0/46) or C4a (1/32).

Conclusions: These findings suggest that C3a and C4a may be useful markers of Lyme disease in patients seen shortly after tick-bite, even in those without EM.

Erythropoietin lowers C4a, corrects refractory symptoms and normalizes selected abnormal brain chemistry in Chronic Fatigue Syndrome

Objectives: Chronic Fatigue Syndrome (CFS) is a systemic illness associated with unexplained abnormalities in inflammatory responses, including innate immune system elements alpha interferon and pro-inflammatory cytokines (PIC). Little is known regarding the role of C4a, a powerful inflammatory anaphylatoxin produced by activation of the classical pathway of complement, as part of the innate immune response in CFS. Clinical data in over 1000 patients seen at one site documented the common occurrence of elevated C4a in CFS patients. Because use of low doses of erythropoietin (epo) safely lowered levels of C4a in other illnesses associated with elevated levels PIC, we hypothesized that (1) low doses of epo would lower symptoms and C4a safely in CFS patients; and that (2) lowered C4a would be associated with durable reduction of symptoms following cessation of therapy (3) reacquisition of symptoms would be associated with a repeat rise in levels of C4a.

Methods: 60 patients with CFS and C4a agreed to take low doses of epo in an off-label study. Symptoms were recorded before each dose of 8000 units of epo, given for 5 doses over 15 days, as was evaluation for adverse effects. C4a levels were drawn at the conclusion of the 5-dose regimen. Patients were classified as either non-responders or improved. Improved cases were observed for relapse in symptoms for 3 months. Improved patients were classified as relapsed or non-relapsed by symptoms. Repeat C4a levels were drawn in improved cases at three months.

Results: No adverse events occurred aside from soreness at the injection site in 10% of patients. 51 patients noted symptom reduction with epo; 9 did not. Of the improved patients, 34 relapsed; 17 were non-relapsed. C4a levels at entry showed differences: mean levels in non-responders were 19,500 (normal < 2830); responders 8200, with reduction to 11,300 and 3200 respectively. In the relapsed group, mean C4a rose to over 12,500 and in the non-relapsed group C4a was 3400.

Conclusions: Use of low dose epo in CFS patients in a short clinical trial safely lowered symptoms and improved levels of C4a in responders. Failure to lower C4a adequately or reacquisition of elevated C4a was associated with ongoing presence of symptoms. Maintenance of lowered C4a was associated with improved quality of life. A double blinded, placebo controlled trial is planned.

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

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.

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Treatment of CFS patients with low levels of vasoactive intestinal polypeptide (VIP) and shortness of breath with tadalafil improves dysfunctional pulmonary artery responses to exercise and exercise tolerance.

Objectives: Recent literature has supported the concept that elevated pulmonary artery pressure (PAP) is lowered by use of tadalafil, a phosphodiesterase-4 inhibitor. PAP should fall with exercise, improving pulmonary venous return to the left atrium. Stress echocardiography provides an indirect measure of PAP by measuring changes in the tricuspid jet. CFS patients were shown to commonly not show a reduction in PAP with exercise. We hypothesized that (1) the increased incidence of dyspnea with exercise seen in CFS patients could be improved by lowering PAP using tadalafil and (2) a rise in VIP levels would be associated with reduction of PAP and symptoms of exercise intolerance.

Methods: 30 male patients with CFS provided informed consent for an off-label study of tadalafil given 20 mg each every three days for 5 doses. Symptoms of shortness of breath, dyspnea and fatigue; levels of VIP; and echocardiographic measures of PAP were compared before and after treatment with 5 doses of tadalafil given by the study physician over 3 weeks. Symptoms were recorded at each visit, as was a review of possible adverse effects. PAP and VIP were measured after the last dose of tadalafil.

Results: No adverse events occurred aside from headache in 16% that did not prevent finishing the tadalafil protocol. Change in erectile behavior was noticed in 93%. Symptom reduction occurred in 90%; PAP showed improvement in 83%. VIP levels rose in 66%.

Conclusions: Use of tadalafil in male CFS patients in a short clinical trial safely lowered dyspnea and improved exercise tolerance concomitant with an improvement in pulmonary artery response to exercise. Tadalafil, a phosphodiesterase inhibitor, causes an increased intracellular level of cGMP, which in turn can lower PAP and improve erectile function in males. The increase in levels of VIP suggests a central effect of tadalafil, which in turn would result in increased intracellular levels of cAMP. The role of cAMP in CFS is not known, but this study provides Symptom improvement could be confounded by sexual side effects of tadalafil but improvement in PAP and VIP suggests the symptom reduction is not coincidental. A double blinded, placebo controlled trial in males is planned.

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