



## **RETROSPECTIVE STUDY OF 400+ CFS/FM PATIENTS FOR IMMUNE SYSTEM ANTIBODY PRODUCTION, ACTIVATION OF COAGULATION, AND HEREDITARY COAG DEFECTS AS PREDISPOSITION FOR CFSIFM.<sup>1</sup>**

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**OBJECTIVE:** The objective of this study is to look at a large data base of patient results for **activation of the coagulation system due to immune system antibody production from a pathogen source and the hereditary defects that would allow inappropriate thrombin generation resulting in soluble fibrin production and fibrin deposition on endothelial cells in the microcirculation.**

**METHODS:** More than 400 patient results were examined in the ISAC Panel (Fibrinogen, Prothrombin Fragment 1+2, Thrombin/Antithrombin Complexes, Soluble Fibrin Monomer, and Platelet Activation by Flow Cytometry), Hereditary Thrombosis Risk Panel [ (AntiThrombin, Protein C, Protein S, APC Resistance, Factor 11, Lp(a), PAI-1, & Homocysteine) and antibody production (Anti-B2-GP I Antibodies) to determine the extent of coagulation activation, antibody production and type of protein defects in this patient population.

**MODEL:** The hypercoagulation model states that one or more pathogens invade through mucous membranes, triggering antibody formation that results in Anti-B2-GPI antibody formation which reacts and removes protective proteins from the surface of endothelial cells (EC) in the capillary beds. In turn, coagulation proteins bind to the EC surfaces, generating excess thrombin (ha). If ha is not removed properly (T/AT complexes), ha converts Fibrinogen to Soluble Fibrin (SFM), increasing blood viscosity and forming fibrin deposition on EC surfaces. Fibrin deposition leads to an anaerobic environment within the EC, blocking oxygen and nutrient passage to tissues around the capillaries, resulting in focal ischemia. Excess thrombin may be generated due to a coag protein defect involving control of thrombin generation. Once fibrin is deposited on EC surfaces, a fibrinolysis protein defect may block the breakdown of fibrin, resulting in hypofibrinolysis and long term oxygen and nutrient deficiencies. This model explains why some patients respond to anticoagulation therapy, which controls excess thrombin generation.

**B<sub>2</sub>Antibodies:** 39/100 (39 %) of patients have positive Anti-B2-GP1 antibodies at time of testing.

**ISAC Panel:** 328/417(79%) of patients have positive ISAC Panels, defined as 2 or more tests positive out of 5. Another 79/417 (19%) had positivity for one assay, for a total of 98% detection rate. Patients receiving IV therapy may have 0 or 1 test positive if tested within 5 days of the therapy.

**HTRP Panel:** 141/175 (81%) of patients have positive HTRP Panels, indicating a coag protein defect as defined in the model. 74/175 (42 %) of patients had defects in control of thrombin (**thrombophilia**), 90/175 (51%) of patients had fibrinolysis defects (**hypofibrinolysis**) and 36/175 (21 %) of patients had **combined defects in both thrombophilia and hypofibrinolysis**. 50/175 (29%) of patients demonstrated **increased levels of AT, Protein C &/or Protein 5, indicating a compensation mechanism** in an attempt to decrease the hypercoagulable state. 4/34 (12%) of the normal HTRP results had demonstrable

compensation mechanism, indicating a hypercoagulable state even though there was no major protein defect found. Of the 39 % of patients with demonstrable antibodies, 25/39(64 %) of patients had increased SFM. 35/39 (90%) were positive for 2 or more ISAC tests, which meets the criteria for pathogen induced AntiPhospholipid Syndrome (APS) [ anticoagulants] as a diagnostic ICD9 code.

**CONCLUSION:** Pathogen(s) induced a hypercoagulable state, SFM and fibrin deposition in CFS/FM patients. 81% of these patients have abnormal regulatory proteins in their coagulation system when tested for the eight major regulatory proteins. This does not include another 8 minor proteins that are involved in coagulation regulation. This explains chronic illnesses based on a coag defect and why anticoagulant therapy works in many of these patients. The high percentage (>50%) of patients with hypofibrinolysis defects (inability to clean up fibrin deposition in the capillaries) explains why some patients have difficulties in returning to health. Trials of low dose fibrinolysis activators (tPA) will begin this year to treat hypofibrinolysis patients. Concurrent therapy for the pathogen(s) is necessary to reduce activation of the coagulation system and to return patients to health.

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