

# Chronic fatigue syndrome and/or Fibromyalgia as a variation of Antiphospholipid antibody syndrome: an explanatory model and approach to laboratory diagnosis

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Chronic Fatigue and/or Fibromyalgia have long been diseases without definition. An explanatory model of coagulation activation has been demonstrated through use of the ISAC panel of five tests, including, Fibrinogen, Prothrombin Fragment 1+2, Thrombin/ AntiThrombin Complexes, Soluble Fibrin Monomer, and Platelet Activation by flow cytometry. These tests show low level coagulation activation from immunoglobulins (Igs) as demonstrated by Anti-B<sub>2</sub>GPI antibodies, which allows classification of these diseases as a type of Antiphospholipid antibody syndrome. The ISAC panel allows testing for diagnosis as well as monitoring for anticoagulation protocols in these patients. *Blood Coag Fibrinol* 10:435-438 © 1999 Lippincott Williams & Wilkins.

**Keywords:** Chronic Fatigue Syndrome, Fibromyalgia, Antiphospholipid Antibody Syndrome, Immune System Activation of Coagulation (ISAC), Anti-B<sub>2</sub>GPI Antibodies, Fibrinogen, Prothrombin Fragment 1+2, Thrombin/AntiThrombin Complexes, Soluble Fibrin Monomer, and Platelet Activation by flow cytometry.

## Introduction

Chronic fatigue syndrome (CFS) and Fibromyalgia (FM) have been considered diagnoses of exclusion where no other diagnosis fits well. In 1987, the American Medical Association recognized FM as a major cause of disability [1]. In 1994, CFS was defined by specific requirements of fatigue, duration, associated symptoms, initial clinical and laboratory evaluation, and medical or psychiatric exclusions. At the most recent meeting of the American Association of Chronic Fatigue Syndrome, the prevalence, prognostic factors, pediatric and adult population studies, potential causal organisms, disruption of normal body functions, autoantibody identification and psychological implications were presented. Antiphospholipid antibody syndrome (APS) [2] is defined by both laboratory and clinical findings. Laboratory findings include anticardiolipin antibodies, lupus anticoagulants, antiphosphatidylserine antibodies, anti-B<sub>2</sub>GPI antibodies, and clinical findings of thrombocytopenia, neurological complications, venous thrombosis, arterial thrombosis, and / or recurrent fetal loss. Patients with primary APS have no clinical or laboratory evidence of another definable autoimmune disease. Antiphospholipid (APL) antibodies have been long associated with a hypercoagulable state, involving both procoagulant activity as well as inhibition of anticoagulant and fibrinolytic activity [3].

In CFS and/or FM patients, the principal anti- bodies found to date are the anti-B<sub>2</sub>GPI antibodies (unpublished data). This precedes the generation of a hypercoagulable state based on our proposed model. Endothelial cells are protected in the micro- vascular circulation by B<sub>2</sub>GPI and Annexin V proteins. This protective layer helps endothelial cells (ECs) maintain an anticoagulant environment. Exposure to pathogens, such as herpes viruses (HV) (HHV6, EBV), cytomegalovirus (CMV), mycoplasma and chlamydia pneumonia, result in both active persistent infection [4] and latency in mononuclear and EC cells [5]. Some pathogens like CMV and HV constitutively express phosphatidylserine like procoagulant activity, capable of binding Xa and Va to form the prothrombinase complex [6]. HHV6 is found in about 70% of all CFS patients [7]. In several studies, this same 70% infection rate is seen in Multiple Sclerosis patients with HHV6 [8]. HHV6 is also implicated in chronic myelopathy. Endothelial cells serve as a reservoir for harboring HHV6 [9]. Infected ECs lose their ability to synthesize prostacyclin with associated incapacity to deter platelet adhesion [10]. In addition, CMV and HV express tissue factor antigen on each virus surface [11]. HV can induce a prothrombotic phenotype in vascular ECs [12]. This phenotype markedly reduces heparan sulfate proteoglycan synthesis and surface expression by ECs. Thrombomodulin expression is also reduced in infected endothelium. Activation of EC is seen by surface expression of, P-selectin and von Willebrand Factor (vWF). Thrombin generated after the assembly of the prothrombinase complex on the virally infected endothelium mobilizes vWF from the Weibel-Pa-lade body to the EC surface, where it acts as a platelet receptor. Cell-independent thrombin generation may be the earliest event in vascular pathology mediated by HV [13].

Since exposure and expression of phosphatidylserine (PS) is part of the infectious process, these exposed phospholipids activate the immune system to form Antiphospholipid antibodies. The primary targets of these immunoglobulin (Ig)G, IgM and IgA antibodies are the protective proteins for ECs, specifically B<sub>2</sub>GPI and Annexin V. Both proteins bind to cells via Ca<sup>2+</sup> binding [14], just as the vitamin K dependent coagulation factors. In pregnancy loss, hypercoagulability may be due to the reduction of surface bound Annexin V by APL antibodies [15]. As in other

APS diseases, there is an increased incidence of thrombocytopenia in HHV6 patients. With the loss of this protective layer due to APL antibodies, coagulation proteins can bind, react and form thrombin (IIa). If this process is not properly inhibited (thrombin-anti-thrombin complexes), then excess thrombin can convert fibrinogen to soluble fibrin monomer (SFM). SFM is a sticky protein that increases blood viscosity and can coat EC surfaces as fibrin or fibrinoid material. The explanation of why one person may become chronically ill and another patient recover when both are exposed to the same pathogen comes in part from the dental community. Glueck *et al.*, have identified that 73% of patients with neuralgia- inducing cavitation osteonecrosis have some form of genetic predisposition for thrombophilia or hypofibrinolysis [161, including: APC resistance, anticardiolipin antibodies, protein C or protein S deficiencies, increased Lp(a) or PAI-1, or decreased tPA activity. These patients responded well to oral anticoagulant therapy.

## Model

Our hypothesis is that a majority of individuals diagnosed as CFS and/or FM on clinical criteria may be defined as APS with the EC as the disease target with or without platelet activation. These patients have a hypercoagulable state, demonstrated by increased markers of coagulation activation and increased blood viscosity due to the generation of SFM. Because the CFS-FM process may be triggered by a variety of pathogens, we suggest that pathogen-mediated immune activation may induce antibodies, e.g. anti-B2GPI, anti-Annexin V antibodies that dislodge protective proteins from EC surfaces, thereby exposing PS on the EC surfaces in capillary beds. This PS exposure would allow binding of the coagulation tenase and prothrombinase complexes to EC surfaces, with subsequent thrombin generation, SFM formation and low level fibrin deposition that could create local pathology by blocking nutrients and oxygen delivery in the microcirculation.' A hereditary defect in a coagulation regulatory protein, such as protein C, protein S, VL, Factor Prothrombin gene mutation, PAI-1, Lp(a), or elevated Homocysteine is probably predispositional. Because this hypercoagulability does not result in a thrombosis, but rather in fibrin deposition, we suggest that an appropriate name for this Antiphospholipid antibody process would be immune system activation of coagulation (ISAC) syndrome. This model provides an explanation for the therapeutic benefits reported with low-dose anti-coagulant therapy (heparin followed by warfarin) in the majority of CFS-FM patients.

Table 1. ISAC panel test data of controls and patients

Test	<i>n</i>	Fibrinogen (mg/dl)	F1+2 (nmol/l)	T-AT (,ug/l)	SFM (nmol/l)	Platelet activation	CD62P (%)
Reference range		< 310	< 1.1	1.0-4.1	< 20	Normal	< 26
Controls	23	280	1.0	1.6	10	0% positive	17.5
#Abn/n		2/23	3/23	4/23	3/23	0/23	5/23
Patients	54	367	1.2	1.6	22	42% positive	22
#Abn/n		45/54	26/54	25/54	32/54	22/52	21/52
P Value		< 0.001	< 0.005	< 0.005	< 0.001	< 0.001	< 0.10

F1 + 2, Prothrombin fragment I + 2, T-AT, thrombin-anti-thrombin complex; SFM, soluble fibrin monomer.

## Results

At the American Association of Chronic Fatigue Syndrome meeting, we presented a retrospective study of 20 patients looking at a hypercoagulable state that could be reversed with anticoagulant therapies [17]. Since then, we have conducted a blinded prospective study of 54 CFS and/or FM patients and 23 controls, using a panel of five tests to determine if patients could be differentiated from controls. The tests included: fibrinogen, Prothrombin fragment I + 2, thrombin-anti-thrombin complexes, SFM and platelet activation by flow cytometry using CD62P and ADP with mean values for each group shown in Table 1. The criterion to separate patients from controls was positivity in two or more assays for classification as a patient. The P value for laboratory diagnosis based on this criterion was < 0.001. Diagnostic data were obtained after all laboratory studies were completed. Twenty-two of the 23 controls were correctly identified. One control was positive in two assays for a false positivity rate of 4%. Of the 54 patients, four had normal values, for a false negative rate of only 7.4%. This shows that greater than 92% of CFS and/or FM patients had a demonstrable hypercoagulable state. What then is the underlying disease process?

## Conclusions

CFS and/or FM patients who have a hereditary deficiency for thrombophilia or hypofibrinolysis may be unable to control thrombin generation properly. We have found that three out of four CFS and/or FM patients have a genetic deficiency (unpublished data). Certain pathogens induce the immune system generation of APL antibodies and can be a triggering mechanism for APS. Once antibodies are formed, protective proteins are dislodged from endothelial cells, exposing PS. Coagulation proteins bind on exposed PS surfaces, generating thrombin on the EC surface. Excess thrombin converts fibrinogen to SFM, which may be deposited on the EC surface and/or circulate in the plasma. Fibrin deposition leads to decreased oxygen, nutrient and cellular passage to tissues around the microcirculation. This hypercoagulable state may cause localized pathology in many tissues, yielding the systemic compromises and symptoms characteristic of the CFS-FM complex. Since this hypercoagulable state does not necessarily result in a thrombosis, but rather in fibrin deposition, we suggest that an alternative name for this Antiphospholipid antibody process would be immune system activation of coagulation (ISAC) instead of antibody-mediated thrombosis [18]. Once this hypercoagulable state is detected, appropriate anticoagulant therapies may be given to relieve patient symptoms. These studies will be presented in a separate report.

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