APC Resistance May Trigger Clotting in Lupus

BY BARBARA RUTLEDGE
Contributing Writer

Acquired resistance against activated protein C may play a key role in increasing the risk of thrombosis in patients with systemic lupus erythematosus, reported Dr. Eelco Meesters of Slotervaart Hospital in Amsterdam and colleagues.

Compared with the general population, patients with systemic lupus erythematosus (SLE) experience a higher incidence of venous thromboembolism, but the underlying mechanism leading to increased risk has not been well defined. Predicting which SLE patients are at greatest risk has been challenging. "An APC [activated protein C] resistance assay may provide an important tool for risk stratification," wrote Dr. Meesters, "but this assumption needs to be tested in prospective studies."

Dr. Meesters and colleagues hypothesized that molecular cross talk between inflammatory pathways and coagulation pathways could be a mechanism underlying the increased risk of arterial and venous thrombosis in patients with SLE. They designed a case-control study to examine the profiles of markers of inflammation, endothelial cell condition, and blood coagulation in patients with SLE versus healthy individuals without SLE, matched for age and gender (Blood Coagul. Fibrinolysis 2007;18:21-8).

In the study, 25 women with SLE (mean age 41.7 years) were matched with 25 healthy women (mean age 41.4 years). As expected, the SLE patients had significantly higher levels of chronic inflammatory mediators, such as C-reactive protein and interleukin-6, and had higher erythrocyte sedimentation rates, compared with controls. Levels of soluble vascular cell adhesion molecule (VCAM)–1 were significantly higher in SLE patients than in controls, but the two groups showed no significant differences in E-selectin or von Willebrand's factor, both markers of endothelial cell activation. Cases and controls were comparable in leukocyte count, hemoglobin level, and cholesterol levels, including total cholesterol, HDL cholesterol, and LDL cholesterol.

The two groups showed significant differences in protein S, a glycoprotein that plays a key role in coagulation. Protein S circulates in human plasma in both a bound state and a free state. In the bound state, protein S interacts in the complement pathway, forming a tight complex with C4b-binding protein. In the free state, protein S functions as an essential cofactor of APC, facilitating the inactivation of coagulation factors Va and VIIIa. Genetic deficiencies in protein S increase the risk of thrombosis, with venous thromboembolism being the primary clinical manifestation of the genetic disorder.

Free protein S levels were significantly lower in SLE patients, compared with controls (68% plus or minus 19 vs. 90% plus or minus 16; $P < .001$), although total protein S levels were comparable in the two groups (107% plus or minus 30 vs. 113% plus or minus 19), ruling out the possibility of a genetic deficiency in protein S in SLE patients.

One likely explanation of the low levels of free protein S in SLE patients compared with controls is that the SLE patients had elevated levels of C4b-binding protein, as previous studies had demonstrated. Higher levels of C4b-binding protein would lead to a greater proportion of total protein S sequestered in the bound form. Thus, the effect on the coagulation pathway would be a decrease in the amount of free protein S available to function as an APC cofactor in anticoagulant activities.

APC resistance, defined as a poor response to the anticoagulant activity of APC, leads to a hypercoagulable state that puts the individual at increased risk for venous thromboembolism. APC resistance can be genetic, resulting from factor V Leiden mutation, or acquired. Resistance to APC was measured using both an endogenous thrombin potential–based (ETP-based) assay and an activated partial thromboplastin time–based (aPTT-based) assay. With each assay, normalized APC sensitivity ratios were significantly different between the cases and controls, indicating APC resistance in the SLE patients.

"Apparently this increased APC resistance is due to acquired factors in the plasma from SLE patients," wrote Dr. Meesters. "The combination of a lowered free protein S level, subsequent to inflammatory activity and raised C4b-binding protein, and to antiphospholipid antibodies, are most probably responsible for this acquired thrombophilic phenotype." ■