Archives of Medical Research 47 (2016) 573–579

Archives of Medical Research

ORIGINAL ARTICLE

Effects of Disease Activity and Inflammatory Response on Hypercoagulability in Patients with Systemic Lupus Erythematosus

Yan Liang, Rui-Xue Leng, Hai-Feng Pan, and Dong-Qing Ye

Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, Hefei, Anhui, PR China

Received for publication August 8, 2016; accepted November 30, 2016 (ARCMED-D-16-00495).

Background and Aims. The aim of the study was to (1) investigate the possible relationships of clinical manifestations and laboratory abnormalities with hypercoagulability in systemic lupus erythematosus (SLE) patients; (2) analyze the interaction effect between SLE disease activity and erythrocyte sedimentation rate (ESR) as well as between C3 and ESR on hypercoagulability.

Methods. The medical records of 1677 SLE patients were collected. Data on demographic characteristics, clinical manifestations, laboratory abnormalities and immunosuppressive agents use were obtained by medical record review. Coagulation score was calculated based on D-dimer and fibrinogen.

Results. Coagulation score was associated with the presence of lupus nephritis (β-coefficient [β]: 0.046; 95% confidence interval [CI]: 0.021−0.071; $p < 0.001$), pleuritis (β: 0.113; 95% CI: 0.074−0.151; $p < 0.001$), pericarditis (β: 0.075; 95% CI: 0.031−0.119; $p = 0.001$), fever (≥38°C) (β: 0.119; 95% CI: 0.083−0.155; $p < 0.001$), active disease (β: 0.070; 95% CI: 0.044−0.096; $p < 0.001$) and increased ESR (β: 0.199; 95% CI: 0.171−0.226; $p < 0.001$) in multivariate linear regression models. A significant effect on coagulation score by the interaction between SLE disease activity and ESR was found ($p < 0.001$). In contrast, there was no significant interaction effect between C3 and ESR ($p = 0.248$).

Conclusions. Lupus nephritis, pleuritis, pericarditis, fever (≥38°C), active disease and increased ESR were associated with hypercoagulability in SLE. There was a significant interaction between active disease and increased ESR for hypercoagulability in SLE.

Key Words: Systemic lupus erythematosus, Hypercoagulability, Disease activity, Erythrocyte sedimentation rate.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the production of autoantibodies and a heterogeneous clinical presentation (1). SLE predominantly affects women of childbearing age, with a female-to-male ratio of ~9:1 (2). It has been recognized that patients with SLE are at high risk of thrombosis and atherosclerosis (3). The pathogenesis of the vascular disease in SLE still remains unclear, but available evidence indicates that dysregulation of the coagulation system could cause initiation of the disease as well as its evolution (4). D-dimer and fibrinogen are two crucial biomarkers for the coagulation system. Elevated plasma D-dimer and fibrinogen levels were observed in the patients with SLE, which have been shown to be independent risk factors for vascular events (5,6).

The dysregulation of the coagulation system may be caused by organ damage in some clinical conditions. A study including 66 stage 4−5 chronic kidney disease (CKD) patients and 36 healthy controls reported that up-regulation of the tissue factor (TF), coagulation factor 7 (F7) and prothrombin fragment 1+2 (F1+2) as well as

Address reprint requests to: Dong-Qing Ye, MD, Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei, Anhui, 230032, PR China; Phone: (+86) 551 65167726; FAX: (+86) 551 65161171; E-mail: ydq@ahmu.edu.cn.

0188-4409/$ - see front matter.
http://dx.doi.org/10.1016/j.arcmed.2016.12.001

significant reductions in anti-thrombin III (ATIII) and the ratio of free protein S (PS):total PS were detected in the patients (7). Another study of 67 patients with stages 3–5 CKD and 90 healthy controls found that the levels of soluble thrombomodulin (sTM) were significantly higher in patients with CKD and this coagulation factor level was positively correlated with disease severity as evidenced by the association between sTM with estimated glomerular filtration rate (eGFR) as well as serum creatinine (8). These data provide a potential link between hypercoagulability and CKD. Further, Lidia et al. (9) investigated the levels of several anti-coagulation factors in 215 European stage 5 CKD patients and the rate of correction of these factors after renal transplantation. They found that, after transplantation, dysregulation of anti-coagulation factors including ATIII, protein C (PC) and PS had disappeared. Similarly, Mangalathillam et al. (10) studied the levels of the anti-coagulation factors in 82 Asian patients with end-stage renal disease who underwent renal transplantation. They found that deficiencies in PC, PS, ATIII and activated protein C resistance (APCR) were completely corrected in all subjects. Collectively, these data suggested that impaired renal function is causally related to hypercoagulability. Apart from kidney damage, vasculopathy may also play a role in the dysregulation of the coagulation system. Ma et al. (11) investigated the coagulation index profiles in 321 anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) patients in active stage and 78 AAV patients in quiescent stage. The results indicated that the circulating levels of D-dimer and fibrin degradation products were significantly higher in AAV patients in active stage. Moreover, circulating levels of D-dimer are associated with disease activity as demonstrated by the fact that compared with patients with normal levels of D-dimer, patients with elevated D-dimer levels had significantly higher levels of serum creatinine, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and the Birmingham Vasculitis Activity Scores. Similar results were also revealed in studies by Salmella et al. (12). This study including 21 AAV patients and 40 controls reported that F1+2, D-dimer, F8 and von Willebrand Factor (VWF) were the highest among the patients with active disease and remained elevated under remission (12). These data provide a potential link between hypercoagulability and vasculitis.

It has become apparent that inflammatory responses can lead to hypercoagulability through concurrent activation of coagulation factors and impairment of anticoagulant mechanisms. For instance, interleukin (IL)-33, an inflammatory cytokine, could promote thrombus formation in the setting of atherosclerosis through induction of TF (13). In addition, during sepsis, the PC system is impaired as a result of decreased production of PC, increased consumption of PC and decreased activation of PC, a direct consequence of tumor necrosis factor (TNF)-α (14). As is known, SLE is a potentially fatal connective tissue disorder characterized by organ damage including kidneys, lung, skin, and central nervous system, with high levels of pro-inflammatory cytokines (1). However, the contribution of organ damage and inflammatory responses to hypercoagulability in SLE is unknown. In this study, we investigated the possible relationships of clinical manifestations and laboratory abnormalities with hypercoagulability in SLE patients. The interaction effects between SLE disease activity and inflammatory biomarker ESR as well as between C3 and ESR on hypercoagulability were also analyzed.

Materials and Methods

Patient Recruitment

This retrospective study recruited patients receiving care at the First Affiliated Hospital of Anhui Medical University and Anhui Provincial Hospital during 2011–2015. Inclusion criterion was patients who fulfilled at least four of the 1982 revised American College of Rheumatology (ACR) classification criteria of SLE, which include malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurologic disorder, hematologic disorder, and immunologic disorder (15). Exclusion criteria were patients who had surgery, pregnancy, malignancy, hepatic diseases and/or vascular diseases within a month of recruitment. Hepatic diseases were objectively verified in each case and defined as follows: autoimmune hepatitis, viral hepatitis, cirrhosis, and/or liver injuries induced by intoxication or drug abuse. Vascular events were defined as follows: 1) ischemic heart disease (IHD): myocardial infarction (MI), confirmed by electrocardiography and an increase in plasma creatine kinase, muscle and brain fraction (CK-MB) or troponin T and/or angina pectoris confirmed by exercise stress test; 2) ischemic cerebrovascular disease (ICVD): stroke including cerebral infarction confirmed by CT or MRI and/or transitory ischemic attacks defined as transient focal symptoms from the brain or retina with a maximum duration of 24 h; 3) ischemic peripheral vascular disease (IPVD): intermittent claudication and/or peripheral arterial thrombosis or embolus confirmed by angiogram or Doppler flow studies; 4) venous thromboembolism: deep vein thrombosis confirmed by venography or ultrasonography and/or pulmonary embolism confirmed by radionucleotide lung scanning or angiogram. With any vascular event, we refer to the occurrence of one or more of 1–4 (16). With these criteria, a final sample of 1677 SLE patients contributed to the analyses. Data on age ($<$36 years or $\geq$36 years), sex (male or female), disease duration (new-onset or relapse) and immunosuppressive agent use (use in the past month or not) were collected. New-onset SLE was identified when the following criteria were met: (1) first-time diagnosis of SLE; (2) no history