Role Of Protein C and S In Neurological Disorders In children With Sickle Cell Disease - Marwa Yassien Badr - Tanta University, Egypt

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Abstract

Background: Patients with sickle cell disease (SCD) have a hypercoagulable state with increased risk of various neurological complications including: headache, cognitive difficulties, seizures, visual loss, ischemic and hemorrhagic stroke, transient ischemic attacks, altered mental status and covert or silent infarction. The purpose of this study is to assess neurological disorders in pediatric patients with SCD using multimodal approach through clinical, laboratory, neuroimaging and neurophysiological studies and detect their relation to protein C and protein S. (2) Methodology: This study was conducted on 50 children with SCD and 25 healthy children matched age and sex in Department of Pediatric (Hematology Unit) and Department of Neurology, Tanta University Hospital, Egypt, between April 2016 and April 2018. All subjects were subjected to full history taking, neurologic examination using pediatric neurological sheet, laboratory investigations (including protein C , protein S), neuroimaging including: CT and /or MRI, MRA and/or CT angiography, also MRV, EEG and Stanford-Binet Intelligence scales-Fifth Edition. (3) Results: SCD patients showed many abnormalities on neurological examination and on different modalities of MR imaging on the brain with positive relation with many risk factors including decreased level of protein C and S. Prophylactic blood transfusion in SCD patients with abnormal TCD had a role in reducing the incidence of stroke. (4) Conclusion: There was variation in neurological presentation, examination and brain imaging in cases with SCD. There was positive relation between decreased level of protein C and S, in SCD cases and increased risk for ischemic and hemorrhagic stroke. There was positive relation between regular blood transfusion in SCD patients and decreased risk for ischemic stroke. Reduced activity of naturally occurring anticoagulants (NOAC) protein C and protein S may contribute to vaso-occlusion in sickle cell disease (SCD). We studied whether protein C and S are related to clinical vaso-occlusion, hematological markers of disease severity (hemoglobin levels, leukocyte counts, and percentage of fetal hemoglobin), and inflammation in SCD. Protein C activity, protein S (free and total) antigen, endothelial activation markers (soluble vascular cell adhesion molecule-1 [sVCAM-1], von Willebrand antigen [vWF]), and high sensitive C-reactive protein (hsCRP) levels were measured in 30 HbSS and 20 HbSC patients and in race-matched HbAA controls. NOAC levels were reduced in patients, and endothelial activation markers and hsCRP were elevated (except vWF in HbSC patients). Protein C activity and vWF levels were lower in HbSC patients who experienced painful crises compared to HbSC patients who were clinically asymptomatic. No other differences were observed between patients who did and did not experience vaso-occlusive events (painful crises, stroke, acute chest syndromes) or leg ulcers. A significant positive correlation between total protein S with hemoglobin levels and a significant negative correlation between total and free protein S and sVCAM-1 were detected in HbSS patients. Except perhaps for protein C in relation to painful crises in HbSC patients, these markers were not associated with the occurrence of clinical events. The protein S, hemoglobin, and sVCAM-1 associations may suggest decreased endothelial protein S production due to the more severe endothelial perturbation in HbSS patients with lower hemoglobin levels. Vascular occlusion has a central role in the pathophysiology of sickle cell disease (SCD) and, although there is little evidence that thrombosis alone is responsible, patients with sickle cell disease are known to have an ill-defined but increased thrombotic risk. The most serious complication of this in childhood is stroke which occurs in 7-10% of children and a further 14% have asymptomatic cerebrovascular disease (CVD) on imaging. We have performed a comprehensive profile of coagulation inhibitors and markers of thrombin generation in 96 children (83 nontransfused [NTx] and 13 transfused [Tx]) with steady-state SCD and 18 healthy sibling controls. The levels of protein S (free and total) and heparin cofactor II were reduced in both the NTx and Tx groups compared to controls and protein C and APC resistance ratios were reduced in the NTx group only. Antithrombin levels were not different from controls. Thrombin-antithrombin complexes and prothrombin fragment F1+2 were increased in both patient groups. In the NTx subgroups with or without CVD there were no differences for any of the parameters measured except for lower haemoglobin levels and higher white cell counts in those with asymptomatic CVD.

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