Protein S is a vitamin K-dependent plasma protein that serves as an anti-coagulant factor.\(^1,2\) It exists in human blood plasma in 2 forms: a free form that exhibits anticoagulant activity as a co-factor for activated protein C\(^3\) and a bound form that is inactivated by C4b-binding protein.\(^4\) Protein S deficiency is inherited in an autosomal dominant manner\(^5\) and its prevalence in the general Japanese population is 2.04%,\(^6\) although it accounts for 17.7% of Japanese patients suffering from spontaneous deep vein thrombosis.\(^7\) We report a case of hereditary protein S deficiency with a history of recurrent acute myocardial infarction (AMI).

**Case Report**

In 2000, a 58-year-old man who complained of severe chest pain and dyspnea was brought to Higashi-osaka City General Hospital by ambulance. He was free from any conventional coronary risk factors including cigarette smoking, hyperlipidemia, diabetes mellitus, and hypertension. Auscultation and chest roentgenogram suggested lung edema. His left leg was edematous compared with the right and the skin was brownish in color, suggesting chronic blood congestion in the left leg. In the emergency room sublingual nitroglycerin did not relieve the chest pain and on the electrocardiography there was ST segment depression in leads V4–6 and abnormal Q wave in II, III, aVf, suggesting acute coronary syndrome. Blood testing revealed a significant elevation of creatine kinase (CK) of 737 IU/L, which indicated a novel episode of AMI.

On admission, emergency cardiac catheterization revealed triple-vessel disease (ie, 90% stenosis at the proximal portion of the left anterior descending artery (LAD) with delayed distal filling, 90% stenosis at the proximal portion of the left circumflex artery, and diffuse long 90%
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stent lesions of the right coronary artery). Left ventriculography showed hypokinesis in the anterior wall and akinosis in the inferior wall. Because of the angio graphical delay along the LAD and the abnormal Q wave in leads II, III and aVF, the LAD was thought to be the culprit artery for the current heart attack. Under the support of intra-aortic balloon pumping, the stenotic lesion of the LAD was successfully dilated to less than 25% by balloon angioplasty without angiographical delay. Three days later, his hemodynamic status stabilized without the support of the intra-aortic balloon pumping. The maximal plasma level of CK and its cardiospecific isozyme, CK-MB, after the angioplasty, were 1,801 and 186.8 IU/L, respectively.

Prior to this admission, the patient had suffered from his long history of circulation disorders: deep vein thrombosis in his left leg at 45 years old, brain infarction causing paralysis of his left leg at 46 years old, and inferior myocardial infarction at 52 years old. Similar symptoms were found in his relatives (Fig 1): brain infarction in his mother (I-2), deep vein thrombosis in his elder sister (II-1), deep vein thrombosis and left hemiplegia due to brain infarction in his elder brother (II-2). A congenital abnormality in blood coagulation was suspected in this pedigree. Blood tests performed in 1994 when the patient was 52 years old revealed a low activity of protein S (Fig 1). Since then the propositus had been administered warfarin, an oral anticoagulant, to prevent further circulation disorders.

To confirm the functional abnormality of protein S in the propositus, his blood was sampled 3 months after the second heart attack. To exclude the effect of warfarin on the blood test, it was suspended 2 weeks prior to the blood sampling and during the 2-week suspension, heparin was administered intravenously to reduce the risk of additional sampling and during the 2-week suspension, heparin was administered intravenously to reduce the risk of additional circulation disorders. To exclude the effect of warfarin on the blood test, it was suspended 2 weeks prior to the blood sampling and during the 2-week suspension, heparin was administered intravenously to reduce the risk of additional circulation disorders. Total protein S antigen,1 free protein S antigen,11 and functional protein S activity were measured according to the manufacturer’s instructions (Roche diagnostics, Tokyo). Antithrombin III activity18 functional protein C activity19 and protein C antigen were measured according to the manufacturer’s instructions (Daiiti-kagaku-yukuhin, Sismex, and Iatron Laboratories, Inc, respectively). Although the total amount of protein S antigen was 65% (at the lower limit of normal), the level of free protein S antigen was significantly low (31%). Functional protein S activity was less than 10%. Other factors influencing blood coagulation were within normal range, including anti-thrombin III and protein C (Table 1). Besides the propositus (II-5), blood sample were obtained from II-2, II-6, III-1 and III-2, and protein S deficiency was confirmed in II-2 and III-1 (Fig 1).

Discussion

Hereditary protein S deficiency is a well-known risk factor not only for venous thrombosis but also for arterial thrombosis including AMI10–12 stroke13 and peripheral artery thrombosis14 in those reports, the patients were young or middle aged (17–55 years old) and their coronary arteries appeared to be devoid of organic stenosis although they were occluded with some thrombus10–12 which suggests a crucial role of thrombophilia in the catastrophic growth of thrombus in the intracoronary lumen.

The present patient experienced the first heart attack at age 52 and the second one at age 58 years. Cardiac catheterization showed severe coronary arteriosclerosis (ie, triple vessel disease), although he did not have any conventional coronary risk factors. Because of his long history of deep vein thrombosis, warfarin had been prescribed since he was 52 years old and the prothrombin time test on his present admission revealed an international normalized ratio (INR) of 1.93. This raises the interesting question of whether protein S deficiency is a novel risk factor for the progression of coronary atherosclerosis. Even under warfarin therapy, microthrombi might repeatedly form in the coronary arteries and we suspect that such a process would facilitate the progression of coronary atherosclerosis.

The genetic analyses of patients with protein S deficiency, including that of the propositus, were performed by the single-strand conformational analysis followed by DNA sequencing. Using this technique, 11 unrelated thrombophilic Japanese families with protein S deficiency were investigated and we successfully identified 3 missense mutations in 3 patients with protein S deficiency.7 The mutation in the propositus, however, was not identified, partly because of the presence of the 97% homologous pseudogene. An alternative possibility is that the mutation of the propositus was inversion or a gross deletion of the protein S gene that could not be identified by the polymerase chain reaction method used at that time.

This case report contributes to the better understanding of the role of thrombophilia, including protein S deficiency, in the etiology not only of venous thrombosis but also of arterial circulation disorders.

References


