Different impact of two mutations of a novel compound heterozygous protein C deficiency with late onset thrombosis

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ABSTRACT. We investigated the alteration of coagulation state in a protein C (PC) deficiency pedigree and the impact of the PC gene mutations. The pedigree of a proband with cerebral hemorrhagic infarction had sixteen members with four generations. The plasma levels of PC activity (PC:A), protein S activity (PS:A), factor V:C and factor VIII:C, and routine coagulation tests were measured. Nine exons of the PC gene (PROC) were sequenced. Plasma PC:A and PC antigen (PC:Ag) of the proband were 26 and 18%, respectively, which was significantly lower than normal ranges. Two heterozygous missense mutations of PC in the proband were identified, T>G at site 6128 (exon 7) and G>C at site 8478 (exon 9) resulting in F139V and D255H, respectively. The family members with F139V (N = 4) or D255H (N = 4) had lower levels of PC:A and PC:Ag than members with wild-type
PROC (N = 6). D255H mutation caused a more significant decrease in the levels of PC:A, PC:Ag and factor V:C as compared to F139V mutation (P < 0.05). Two independent mutations, F139V and D255H, of PROC reduce PC function. Compound heterozygous condition of the two mutations can cause synergistic PC deficiency, but resulting in later onset of cerebral thrombosis.

Key words: Compound heterozygous gene mutation; Thrombosis; Protein C deficiency; Pedigree