Familial Cerebrovascular Accidents Due to Concomitant Hyperhomocysteinemia and Protein C Deficiency Type 1

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Background and Purpose: Hyperhomocysteinemia and protein C deficiency are risk factors for thromboembolism. Hyperhomocysteinemia has been reported to inhibit the expression of thrombomodulin and to inactivate both thrombomodulin and protein C irreversibly, leading to decreased protein C activity.

Case Description: In a 16-year-old girl, who developed a sinus sagittalis thrombosis, and in her father, who experienced a transient ischemic attack, both hyperhomocysteinemia and protein C deficiency type 1 were present. Protein C deficiency alone was found in one of the two sisters, who was without any clinical vascular history.

Conclusions: In this family with independently inherited hyperhomocysteinemia and protein C deficiency, clinical cerebrovascular disease occurred only in those members with a combination of both risk factors, suggesting a synergistic interaction between these thrombogenic risk factors. (Stroke. 1993;24:1599-1600.)

Key Words: cerebral infarction • genetics • protein C • thromboembolism

Mild hyperhomocysteinemia has come to be recognized as an independent risk factor for thromboembolic and premature arteriosclerotic complications.1-5 Although the mode of inheritance is not established, there is evidence that mild hyperhomocysteinemia is influenced by genetic factors.6 Protein C deficiency type 1 is a disorder with autosomal dominant inheritance with variable penetrance, in which protein C activity as well as protein C antigen is decreased.7,8 The conversion of protein C into activated protein C is enhanced by the cofactor thrombomodulin. A deficiency of the anticoagulant protein C, in both its hereditary and acquired forms, is also recognized as an independent risk factor for venous and arterial thrombosis.9,10

Homocysteine has been reported in in vitro studies to inhibit thrombomodulin expression on endothelial cell surface and to inactivate both thrombomodulin and protein C irreversibly.11,12 Thus, hyperhomocysteinemia and protein C deficiency are both independent risk factors for thrombotic and thromboembolic complications; furthermore, hyperhomocysteinemia may exaggerate the decrease of protein C activity in case of protein C deficiency.

In this report we present the history of a teenaged girl from a family with inherited hyperhomocysteinemia as well as protein C deficiency type 1.

Case Report

A 16-year-old girl born to nonconsanguineous parents was admitted to our hospital with vomiting, fever, and nuchal rigidity. Penicillin was administered because bronchitis was suspected. After 3 days she developed headache, dysphasia, dysarthria, and a right-sided hemiparesis. Venous and arterial digital subtraction angiography revealed thrombosis of the superior and inferior sagittal sinus and straight sinus. Additionally, a moderate hypercholesterolemia (7.7 mmol/L; reference value, ≤6.0 mmol/L) was detected. She had been smoking approximately two to five cigarettes daily for 3 years and had used sub-50 oral contraceptives containing 35 µg ethinylestradiol and 2 mg cyproteronacetate (Diane-35) for 5 months.

The diagnosis of hyperhomocysteinemia in the index subject and family members was made by means of a standardized methionine loading test as reported previously.13 The plasma total homocysteine concentration immediately before and 6 hours after the methionine loading was analyzed by high-performance liquid chromatography.14 Protein C activity and antigen screening in these persons was performed and analyzed by a previously described method.15

Both hyperhomocysteinemia (19 µmol/L before and 60 µmol/L after load; reference value [mean±2 SD for premenopausal women], 5 to 15 µmol/L and 15 to 49 µmol/L, respectively) and protein C deficiency type 1 (protein C activity, 33%; protein C antigen, 45%;...
reference values, >60% and >70%, respectively) were present in the index patient.

The patient’s 43-year-old father had smoked 20 cigarettes daily since the age of 14 years and had a history of a transient ischemic attack at the age of 40. In addition, both hyperhomocysteinemia (34 μmol/L before and 71 μmol/L after load; reference value [mean±2 SD for men], 7 to 17 μmol/L and 20 to 51 μmol/L, respectively) and protein C deficiency type 1 (protein C activity, 60%; protein C antigen, 58%) were established. The patient’s 39-year-old mother, who had smoked from age 14 to age 33, and two younger sisters (15 and 13 years of age, respectively), both without smoking habits, were without history of vascular complications and did not show hyperhomocysteinemia after methionine loading (13, 13, and 12 μmol/L before load, respectively, and 35, 23, and 24 μmol/L after load, respectively). The protein C activity and protein C antigen in her mother (95% and not measured, respectively) and in one of the two sisters (68% and 74%, respectively) appeared to be normal. However, protein C deficiency type 1 was present in the other sister (protein C activity, 41%; protein C antigen, 47%).

With the exception of the use of tobacco in both parents, there were no further predisposing factors for vascular disease present in the parents and sisters. In particular, no hyperlipoproteinemia, diabetes, or high blood pressure was noted.

Discussion

Cerebral venous thrombosis is often associated with sepsis, dehydration, polycythemia, malignancies, postpartum state, use of oral contraceptives, antithrombin III deficiency, systemic lupus erythematosus, head injury, and Behcet’s syndrome. Both hyperhomocysteinemia and protein C deficiency type 1 are also risk factors for thrombosis.5,6,8 In the studied family both states were independently inherited, and clinical thrombosis occurred only in those family members with hyperhomocysteinemia as well as protein C deficiency type 1. In these subjects the elevated homocysteine concentration may have decreased the protein C activity even more, resulting in a very high risk for thrombosis.

Hyperhomocysteinemia was treated with vitamin B6, 250 mg daily, and the homocysteine concentration decreased to 15 and 37 μmol/L in the index patient and 24 and 57 μmol/L in her father before and after load, respectively. The thrombotic tendency caused by the protein C deficiency was attenuated by anticoagulant therapy in the 16-year-old girl and by salicylate administration in her father. While on this treatment, no further complications as a result of their prothrombinic tendency have occurred during the last 2 years.

The basis of the hyperhomocysteinemia in this family is unclear. Before the performance of the methionine loading test, secondary causes of mild hyperhomocysteinemia had been excluded, such as vitamin B6, B12, and folic acid deficiencies and failure of liver and renal functions. Possible genetic defects in methionine metabolism leading to mild hyperhomocysteinemia are heterozygosity for cystathionine synthase deficiency or homozygosity for thermolabile 5-methyltetrahydrofolate reductase.1,2,17 The determination of these enzyme activities is not performed on a routine basis and was not available in these hyperhomocysteinemic family members. The beneficial effect of homocysteine-lowering treatment with vitamin B6 might suggest the presence of the heterozygosity for cystathionine synthase deficiency in this particular family.

We conclude that screening for hyperhomocysteinemia and protein C deficiency in patients presenting with thromboembolic events of unknown origin is recommended because both factors may independently lead to thrombosis. Moreover, these factors may have a possible synergistic interaction, as indicated in previous in vitro studies.11,12

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References

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