Association of Protein-S Deficiency with Thrombosis in a Kindred with Increased Levels of Plasminogen Activator Inhibitor-I.

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Association of Protein-S Deficiency with Thrombosis in a Kindred with Increased Levels of Plasminogen Activator Inhibitor-I

Charles D. Bolan, MD; Chitra Krishnamurti, PhD; Douglas B. Tang, PhD; Leonthena R. Carrington, BS; and Barbara M. Alving, MD

Objective: A single kindred in North America with various thromboses was described having defective fibrinolysis because of increased levels of plasminogen activator inhibitor-1 (PAI-1). Our study describes the discovery of protein-S deficiency in this kindred and its association with various thromboses.

Design: A family study.

Setting: Community.

Participants: Twenty-eight adults (ages 21 to 71 years) from three generations of the kindred: seven had a history of various thromboses.

Measurements: Plasma levels of total and free protein-S antigen, as well as the activities of protein C, protein S, and antithrombin III.

Results: Six of 7 persons (86%) with a history of various thromboses were deficient in total and free protein-S antigen, while 21 asymptomatic members, 9 were deficient in protein-S antigen (P = 0.03). When compared with controls, 8 persons with protein-S deficiency and a history of thrombosis tended to younger (P = 0.01) and to have higher hypercoagulable levels (P = 0.001). Overall, the mean PAI-1 activity in 7 persons who had thromboses was 7.9 BAU/mL (ALM) and was 5.8 BAU/mL in 21 persons who did not have thromboses (P < 0.001). Conclusion: In this kindred, a deficiency of total and free or functional protein-S is the cause of thromboses. Measurement of PAI-1 activity was not useful in the evaluation of familial thromboses. The utility of the routine measurement of PAI-1 activity in the evaluation of familial thromboses has not been established.
Association of Protein S Deficiency with Thrombosis in a Kindred with Increased Levels of Plasminogen Activator Inhibitor-1

Charles D. Bolan, MD; Chitra Krishnamurti, PhD; Douglas B. Tang, PhD; Leonthena R. Carrington, BS; and Barbara M. Alving, MD

Objective: A single kindred in North America with venous thrombosis was described as having defective fibrinolysis because of increased levels of plasminogen activator inhibitor-1 (PAI-1). Our study describes the discovery of protein S deficiency in this kindred and its association with venous thromboembolism.

Design: A family study.

Setting: Community.

Participants: Twenty-eight adults (ages 21 to 71 years) from three generations of the kindred; seven had a history of venous thromboembolism.

Measurements: Plasma levels of total and free protein S antigen, as well as the activities of protein S, protein C, PAI-1, and antithrombin III.

Results: Six of 7 persons (86%) with a history of venous thromboembolism were deficient in total and free protein S; of 21 asymptomatic members, 9 were deficient in protein S (P = 0.08). When compared with these 9 asymptomatic family members, the 6 persons with protein S deficiency and a history of thrombosis tended to smoke (P = 0.01) and to have higher triglyceride levels (P = 0.001). Overall, the mean PAI-1 activity in the 7 persons who had thrombosis was 7.9 kAU/L (AU/mL) and was 9.3 kAU/L (AU/mL) in the 21 persons who did not have thrombosis (95% CI, 7.0 to 9.9). All 9 asymptomatic family members, the 6 persons with protein S deficiency and a history of thrombosis tended to smoke (P = 0.01) and to have higher triglyceride levels (P = 0.001). Overall, the mean PAI-1 activity in the 7 persons who had thrombosis was 7.9 kAU/L (AU/mL) and was 9.3 kAU/L (AU/mL) in the 21 persons who did not have thrombosis (95% CI, 7.0 to 9.9). Overall, the mean PAI-1 activity in the 7 persons who had thrombosis was 7.9 kAU/L (AU/mL) and was 9.3 kAU/L (AU/mL) in the 21 persons who did not have thrombosis (95% CI, 7.0 to 9.9). Overall, the mean PAI-1 activity in the 7 persons who had thrombosis was 7.9 kAU/L (AU/mL) and was 9.3 kAU/L (AU/mL) in the 21 persons who did not have thrombosis (95% CI, 7.0 to 9.9). Overall, the mean PAI-1 activity in the 7 persons who had thrombosis was 7.9 kAU/L (AU/mL) and was 9.3 kAU/L (AU/mL) in the 21 persons who did not have thrombosis (95% CI, 7.0 to 9.9). Overall, the mean PAI-1 activity in the 7 persons who had thrombosis was 7.9 kAU/L (AU/mL) and was 9.3 kAU/L (AU/mL) in the 21 persons who did not have thrombosis (95% CI, 7.0 to 9.9).

Conclusions: In this kindred, a deficiency of total and free or functional protein S is the cause of thrombosis. Measurement of PAI-1 activity was not useful in the evaluation of familial thrombosis. The utility of the routine measurement of PAI-1 activity in the evaluation of familial thrombosis has not been established.

The most common inherited abnormalities associated with familial venous thrombosis are deficiencies of protein S, protein C, and antithrombin III (1-3). All are inherited in an autosomal dominant manner and can result in venous thrombosis at a young age. The most common of these three deficiencies is protein S, which circulates in a free form and in an inactive complex with C4b-binding protein. Only unbound or free protein S has functional activity as a cofactor for activated protein C in inhibiting factors Va and VIIIa (4). Thus, assessment of patients for protein S deficiency includes measurement of the level or activity of free protein S.

Although assays are now widely available for measuring components of the fibrinolytic system, the importance of decreased fibrinolysis as a risk factor for thrombosis is not well defined (3, 5). Defective fibrinolysis may be due to increased levels of plasminogen activator inhibitor-1 (PAI-1), a specific inhibitor of tissue-type plasminogen activator. Plasminogen activator inhibitor-1 activity can be increased chronically in some persons such as pregnant women (6), or can undergo acute increases of 3 to 40 times in persons who have had surgery (7) or who are septic (8, 9). Increased levels of PAI-1 have been reported as a cause of familial thrombosis in one North American kindred (10, 11) and in two European families (12-15). However, measurements of free protein S were not included in those reports because assays were not yet easily available; further, only symptomatic members were studied.

A re-evaluation of the North American kindred was initiated in 1987, because an asymptomatic family member wanted to know his potential risk for thrombosis. The availability of functional assays for the determination of protein C (16) and protein S (17), as well as the continued clinical interest in the role of PAI-1 in promoting thrombosis, prompted more extensive evaluation of this family in 1991 and 1992. Protein S deficiency was documented in 6 of the 7 adults who had a history of venous thromboembolism and in 9 of 21 asymptomatic family members. Plasminogen activator inhibitor-1 activity was increased in some persons; however, PAI-1 activity and a history of thrombosis were not correlated. Our study provides further evidence that the clinical utility of assays for PAI-1 activity in evaluating familial thrombosis has not been established (3, 5).

Abbreviation
PAI-1 plasminogen activator inhibitor-1


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Figure I.

Generations are in roman numerals, and persons within generations are in arabic numerals. Striped symbols represent persons with a history of thrombosis; black symbols represent persons with protein S deficiency; and white symbols represent persons with no known history of thrombosis. Squares and circles represent men and women, respectively, who were interviewed; diamonds represent living family members not personally interviewed but with no known history of thrombosis according to other members interviewed. Diagonally slashed lines represent deceased persons, and small hash marks represent persons available for laboratory testing.

Methods

Patients

In 1983, a kindred was reported with venous thrombosis attributed to defective fibrinolysis (10). In a subsequent study (11), increased plasma PAI-1 activity was measured in a symptomatic person in the kindred, suggesting that increased levels of the inhibitor were the cause of the defective fibrinolysis and thrombosis.

In 1987, an asymptomatic 40-year-old, military family member (who wanted to know his risk factor for thrombosis [III-26]) and his 39-year-old sibling (III-29) (who had a history of venous thrombosis at age 27 years) were evaluated at the Walter Reed Army Institute of Research. Levels of free and total protein S were decreased in the plasma from the sibling with thrombosis; his plasma PAI-1 activity was normal and the tissue plasminogen activator activity was normal before and after venous occlusion (18). The asymptomatic, active-duty member had normal levels of free and total protein S; however, plasma PAI-1 activity was increased and his tissue plasminogen activator activity was decreased before venous occlusion and did not change after occlusion. These data suggested that protein S deficiency and not increased levels of PAI-1 activity was associated with thrombosis in this family, and further investigation of family members was initiated.

All persons gave informed consent under a protocol approved by the Walter Reed Army Institute of Research Human Use Committee. Evaluations were done in the homes of family members or at the Walter Reed Army Institute of Research and occurred at least 4 months after the most recent thromboembolic event. The age, sex, smoking habits, medications, and medical conditions associated with thrombosis were recorded for each participant. Patients were considered smokers if they smoked cigarettes at the time of their previous thrombotic events. At the time of testing, none of the participants was pregnant or had evidence of recent infection or trauma.

The date, anatomic location, and treatment of previous thromboembolic events were obtained either from family members, their physicians, or review of medical records. Of the seven patients with a history of venous thromboembolism who participated in this study, thromboses had been documented by ventilation perfusion scans or venography or both in all but one patient (IV-1).

The family pedigree (Figure 1) showed a large kindred with a history of thromboembolic events in three generations. Thirty-four adults were interviewed, including all the adult members of the originally reported pedigree (II-7, his spouse II-7s, and their descendants). A total of 28 adults were available for laboratory testing. This included seven surviving persons with a history of thrombosis. In addition, seven asymptomatic children (IV-21, IV-24, IV-25, IV-31, IV-41, IV-42, IV-43) ranging in age from 6 to 17 years were tested for protein S deficiency but were not included in the analysis.

Family History

When the family was first described in 1983 (10), five members had a history of venous thromboembolism. Two brothers (III-26 and III-29) had deep venous thrombosis and pulmonary embolism at ages 25 and 27 years, respectively. A third brother (III-25) died at age 29 years from mesenteric thrombosis and pulmonary embolism, which were confirmed at autopsy. Two sons of III-25 had superficial thrombophlebitis (IV-32) and pulmonary embolism (IV-33) at ages 14 and 13 years, respectively.

Three years after this initial report, the patriarch of the family (II-7), who was then 64 years old, developed deep venous thrombosis, which was confirmed by ultrasound. He agreed to take warfarin for several weeks only and has not had
Protein S

Anticoagulant (9 parts blood: 1 part sodium citrate) and obtained between the hours of 8:00 a.m. and 10:00 a.m. from healthy persons who had fasted for 12 hours and had abstained from smoking and from any form of exertion for at least 1 hour before phlebotomy. Blood was drawn by venipuncture through a 21-gauge butterfly needle, was mixed with 3.8% (weight/volume) trisodium citrate anticoagulant (9 parts blood: 1 part anticoagulant) in a polypropylene tube, and was immediately centrifuged at 12,000 × g in an Eppendorf microfuge 3200 (Brinkman Instruments, Westbury, New York) for 3 minutes at 22 °C. The separated plasma was immediately aliquoted and frozen at −40 °C.

Protein S Assays

Functional protein S activity was determined by measuring its cofactor activity for activated protein C in a modified, activated partial thromboplastin time assay (Staclot Protein S, American Bioproducts, Parsippany, New Jersey). A laboratory reference range (mean ± 2 SD) was determined in 23 healthy men and 22 healthy women who were not pregnant or receiving oral contraceptives. The values were expressed as the percentage of protein S activity in pooled plasma obtained from 18 normal volunteers (9 men, 9 women; 34 ± 13 years [mean ± SD]).

An enzyme-linked immunosorbent assay procedure (American Bioproducts) was used for the immunologic determination of total protein S and of free protein S, which remained in the supernatant after removal of bound protein S with 3.75% polyethylene glycol 8000 (19). The mean ± 2 SD was determined for 20 healthy men and 20 healthy women and was expressed as the percentage of antigen in pooled plasma.

Protein C Assays

In family members with a history of thrombosis, protein C functional activity was determined in clotting assays (Staclot Protein C, American Bioproducts). Laboratory reference ranges (mean ± 2 SD) for functional protein C were determined from 20 healthy men and 20 healthy women and were expressed as a percentage of the activity in normal pooled plasma.

Assays for Fibrinolysis

PAI-1 activity was determined by the method of Chmielowska and colleagues (20) in nonacidified plasma. Tissue plasminogen activator (50 IU/mL) was incubated for 10 minutes with dilutions of plasma in 0.02 mol/L sodium phosphate containing 0.1 mol/L sodium chloride, pH 7.3. After acidification and dilution, residual tissue plasminogen activator activity was determined, as previously described (18, 21). One unit (arbitrary unit) of inhibitor was defined as the amount that inhibits 1 IU of tissue plasminogen activator in 10 minutes at 37 °C. Reference ranges for tissue plasminogen activator and PAI-1 activity, reported for the 10th and 90th percentiles, were obtained in 35 healthy men and 35 healthy women (18).

Other Assays

The β chain-C4b-binding protein (β chain-C4BP) concentration was measured in plasma from four protein S deficient family members by the procedure described by Griffin and colleagues (22).

Von Willebrand factor antigen levels were determined with an enzyme-linked immunosorbent assay (American Bioproducts). The fibrinogen, prothrombin time, activated partial thromboplastin time, thrombin time, antithrombin III activity, plasminogen levels, and factor VIII activity were determined, as previously described (23, 24). Triglyceride levels were measured by enzymatic methods (25).

Data Analysis

Laboratory data are reported as mean values with standard deviations. Because of skewness, the Wilcoxon rank-sum test was used to test for differences in location (medians) between two comparison groups (for example, PAI-1 activity in members with and without a history of thrombosis). Reported 95% confidence intervals (CIs) are for differences in mean values (CIs for differences in median values are qualitatively similar). The Fisher exact test was used to compare two proportions (26). Because of the relatively small sample size of the pedigree, comparisons were not adjusted for possible confounders such as age and sex. All reported P values are two-sided and were not adjusted for possible confounders such as age and sex (27).

Results

In this kindred, the functional assay for protein S and the immunologic assay for free protein S clearly indicated a subgroup of 15 family members (8 men and 7 women) with markedly lower levels compared with the laboratory reference ranges for normal persons (Figure 2). Mean total protein S levels in these persons were decreased to a lesser extent (Table 1). The β chain-C4BP concentration in plasma samples from four protein S deficient patients ranged from 97 to 133 µg/mL (normal range, 86 to 162 µg/mL).

A comparison of clinical data and laboratory results for persons with and without thrombosis (according to the presence of protein S deficiency) is given in Table 1. Six of the 7 persons with thrombosis (86%) were protein-S deficient compared with 9 of 21 (43%) without
Figure 2. Functional and free protein S levels in normal and deficient patients related and not related to the pedigree. Panel A. Patients unrelated to this pedigree. Functional protein S activity and free protein S antigen levels measured by enzyme-linked immunosorbent assay in 45 healthy volunteers (23 men and 22 women) and in 14 patients unrelated to this pedigree with protein S deficiency (10 men and 4 women). The dotted lines are the lower limits of the reference ranges for functional and free protein S for both women and men. Panel B. Functional and free protein S levels in the adult pedigree members. Functional protein S activity and free protein S antigen levels measured by enzyme-linked immunosorbent assay in 27 adult family members. The conversion factor for protein S to SI units is 0.01.

Among persons with protein S deficiency, those who had a history of thrombosis tended to smoke (4 of 6 versus 0 of 9; \( P = 0.011 \)) and to have higher triglyceride levels than did those who were asymptomatic (118 versus 57 mg/dL; \( P = 0.002 \)) (1.33 versus 0.64 mmol/L). Of the symptomatic persons with protein S deficiency, 5 of 6 were men compared with 3 of 9 of the asymptomatic protein S deficient persons (\( P = 0.12 \)). Protein C activity was normal in all persons with a history of thrombosis. Factor VIII and von Willebrand factor antigen levels were moderately increased, as previously de-

<table>
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<td>Factor VIII, %</td>
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<td>PAI-1, ( AU/mL )</td>
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<td>17</td>
<td>3.3 ± 3.3</td>
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<td>Triglycerides, ( mg/dL )</td>
<td>118 ± 29</td>
<td>108</td>
<td>57 ± 23</td>
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</table>

* Values are mean \( \pm \) SD where indicated. The conversion factor to SI units is 0.01 for protein S, protein C, vWF:Ag, and factor VIII. The conversion factor for PAI-1 (kAU/L) is 1 and for triglycerides (mmol/L) is 0.01129. PAI-1 = plasminogen activator inhibitor-1; vWF:Ag = von Willebrand factor antigen.

† As determined by the enzyme-linked immunosorbent assay procedure described in Methods.
scribed (10) but were similar in members with or without thrombosis (see Table 1).

Overall, the mean PAI-I activity in the 7 persons who had thrombosis was 7.9 AU/mL (kAU/L; AU, arbitrary units) and was 9.3 AU/mL (kAU/L) in the 21 persons who did not have thrombosis (95% CI, -9.9 to 7.0; P > 0.2).

In family members with protein S deficiency, mean PAI-I activity was slightly higher in the six members with thrombosis compared with nine without thrombosis (6.3 versus 3.3 AU/mL [kAU/L]; a difference of 3 AU/mL [CI, -2.1 to 8.3; P = 0.22; see Table 1]). Although PAI-I activity tended to be higher in the kindred than in a reference population (18), PAI-I activity among members was highly variable and was not related to a history of thrombosis (Figure 3).

The prothrombin time, activated partial thromboplastin time, fibrinogen levels, and functional plasminogen activity were normal in all persons with a history of thrombosis. Plasma antithrombin-III activity was also in the normal range of 88% to 140% in all but one person (III-25); the value for this person, who also had protein S deficiency, was 74%.

Discussion

Our report documents protein S deficiency in three generations of a kindred with familial thrombosis previously attributed to defective fibrinolysis due to increased levels of PAI-I (10, 11). The data are most consistent with type-I protein-S deficiency in which total as well as free and functional protein-S levels are decreased. Members with protein S deficiency were clearly identified by marked decreases in functional protein S activity and in the concentration of the free protein S antigen. Total protein-S levels, which include functionally active free protein S as well as inactive protein S bound to C4BP, were decreased to a milder degree when measured immunologically in our study.

Protein S binds stoichiometrically to C4BP that contains a β chain (22, 28). The plasma concentration of β chain-C4BP that is available for binding is approximately 264 nmol/L, whereas the concentration of protein S is 346 nmol/L (22). The excess protein S is in the free or functional form. Increased concentrations of β chain-C4BP could bind additional protein S, causing a decrease in the level of free protein S. In this family, β chain-C4BP levels were normal when measured in four persons with protein S deficiency and a history of thrombosis. Thus, the degree of reduction in free protein S was not due to increased levels of β chain-C4BP.

A previous study (29) of six unrelated persons with protein S deficiency found one person with a partial gene deletion that probably resulted in either defective transcription, translation, or secretion. In the other persons, the abnormality could not be identified and may have been due to a point mutation (29). In a more recent study (30), two type-I protein S deficient families were reported to have a variant protein S allele in which a deletion occurred of the exon coding for the N-glycosylation sites (30). The authors of this study postulated that this deletion could result in the production of a nonglycosylated molecule that was either not secreted or underwent rapid clearance from the circulation. The genomic defect in the kindred in our study has not been identified.

Of the 15 adults with protein S deficiency in our kindred, 6 had a history of venous thrombosis that first occurred at a mean age of 28 years. These six persons had statistically higher levels of triglycerides than did the nine asymptomatic protein S deficient persons and were more likely to have a history of cigarette smoking, suggesting that these two factors may be related to an increased risk for thrombosis. The symptomatic persons were more likely to be men, although this was not statistically significant. A similar trend (also not statistically significant) was noted by Engesser and colleagues (31) in a previous study of 12 families with protein S deficiency.

Plasminogen activator inhibitor-1 activity in protein S deficient persons in our kindred with thrombosis was slightly but not statistically increased compared with those without thrombosis. The two members in this study who had the highest PAI-I activity (IV-26 and IV-35) did not have protein-S deficiency and have been asymptomatic.

In a study of 35 patients with protein S deficiency from six families, Engesser and colleagues (32) also found no association between PAI-I activity and thrombosis. In another study (33), the relation between increased PAI-I activity and familial thrombosis was evaluated in 203 young patients with a history of venous thromboembolism. Seven of these patients had persistently increased PAI-1 activity and a positive family history of thrombosis. However, increased PAI-1 activity, which was detected in the families of two of these seven patients, was not associated with a history of thrombosis (33). In a review of the literature, Prins and Hirsh (5) found no convincing evidence for an association between impaired fibrinolytic activity and an increased risk for thrombosis in patients with a history of venous thromboembolism in the nonsurgical setting. However, there was evidence for the association between an increased risk for postoperative thrombosis and impaired fibrinolytic activity measured before and after the operation (5).

The three kindred in which increased PAI-I activity has been implicated as causing familial thrombosis were each first described as having defective fibrinolytic activity before assays for PAI-I had been developed. With the availability of the assays for PAI-I, additional studies were done on selected symptomatic members of these kindred, and levels of PAI-I were felt to be sufficiently increased to explain the defect in fibrinolysis (11, 14, 15). In these follow-up studies, asymptomatic family members were not evaluated. In our study of symptomatic and asymptomatic members of the North American kindred, PAI-1 activity was increased in some persons compared with a reference population (18) but was not associated with thrombosis (see Figure 3).

Plasminogen activator inhibitor-1 has a half-life of approximately 7 minutes in the circulation (34); it is possible that transient increases induced by infection, trauma, or more chronic increases induced by pregnancy could be a factor in promoting thrombosis. How-
ever, correlation of PAI-1 activity with thrombosis is complicated by the circadian variations in PAI-1 activity (35) and the variation in PAI-1 assays done in different laboratories (36). Further, appropriate reference ranges accounting for factors such as age and sex (18) that can also affect PAI-1 activity have not been established. Previous studies, as well as our report, have explored the association between PAI-1 activity and familial thrombosis in a retrospective manner and have examined relatively small numbers of selected patients. At the present time, increased PAI-1 activity has no proven association with familial thrombosis, and its detection does not provide information that can be used to make clinical decisions. Larger, prospective studies are needed to determine the factors that play a role in promoting thrombosis in patients with underlying hypercoagulable states.

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