CORRESPONDENCE

The Accurate Definition of Protein S Deficiency May Avoid the Misestimation of the Frequency of This Defect

To the Editor:

We read with much interest the article by Koster et al. on risk factors for venous thrombosis (VT) in a large patient-control study. Their results confirm those of others who have reported that the deficiencies of protein C (PC) and antithrombin (AT) are risk factors for VT. However, they found slightly more individuals with low protein S (PS) antigen plasma levels in the control group than in the patients and concluded that low PS plasma levels were not associated with an increased risk of VT. Moreover, they noted that women in the control group showed an eightfold higher frequency of low PS plasma levels than did men and that this was not related to the intake of oral contraceptives. Koster et al. accept this sex-related difference in PS plasma levels and suggest that the cut-off point for men and women should be different for the diagnosis of a PS deficiency.

In general, we agree with Koster et al., as do several other investigators who have previously reported on the lower PS plasma levels in women, although an age-dependent difference is not mentioned. As previously reported, we studied 130 healthy donors and showed that women less than 46 years of age had PS plasma levels lower than those of older women and those of men irrespective of their age. These data supported the hypothesis that PS levels are influenced by the female hormonal state. Nevertheless, our subsequent study failed to show a relationship between the estradiol levels and PS concentration, neither in a group of young women during a menstrual cycle nor in a group of women treated with GnRH analogues and gonadotropins. Thus, we think that it is possible that the lower PS levels observed in young women may result from the sum of diverse stimuli on the synthesis and/or metabolism of PS.

In any case, we believe that the normal ranges for total and free PS antigen should be established in two well-defined groups of controls. One group should consist of women aged less than 45 years and another group of women aged more than 46 years and of men of a wide range of ages. Using these control groups should allow the accurate diagnosis of a true PS deficiency. In any case, we believe that the normal ranges for total and free PS antigen should be established in two well-defined groups of controls. One group should consist of women aged less than 45 years and another group of women aged more than 46 years and of men of a wide range of ages. Using these control groups should allow the accurate diagnosis of a true PS deficiency. In any case, we believe that the normal ranges for total and free PS antigen should be established in two well-defined groups of controls. One group should consist of women aged less than 45 years and another group of women aged more than 46 years and of men of a wide range of ages. Using these control groups should allow the accurate diagnosis of a true PS deficiency.

Thus, it may be that the results shown by Koster et al. would have been different if the above-mentioned age-related differences had been considered to define a PS deficiency.

We believe that there is convincing evidence, both from clinical reports and from molecular studies, that a low PS level is a risk factor for VT. This evidence is strengthened by the finding that there are specific mutations in the PS gene that predispose to VT. It now seems safe to conclude that the prevalence of AT, PC, and PS deficiencies in patients with thromboembolic disease is very low. Moreover, further clinical investigations are required before unequivocal data support or deny that these protein deficiencies actually lead to a slightly or strongly prothrombotic state.

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REFERENCES


Response

We thank Falkon et al. for their comments on our finding that, among 474 unselected consecutive thrombosis patients and 474 healthy control subjects, lowered protein S levels were not associated with an increase in thrombosis risk. They suggest that, if we had used age-specific cut-off points for the protein S assay in women, we might have found a different result. We do not think this to be likely, because our study was age- and sex-matched, ie, in the analysis, every female patient was compared with a female control who had the same age (with a maximum difference of 5 years). We found slightly more female controls than female thrombosis patients with lowered protein S levels. This means that, regardless of the cut-off point used, we would have found approximately equal numbers of patients and control subjects with a low protein S value, leading to a relative risk of 1, ie, no excess thrombosis risk for subjects with low protein S levels.
At present, we do not have a satisfactory explanation for our finding, which is in disagreement with many reports of protein S-deficient kindreds. It might be that protein S deficiency is so rare that we did not find a single true heterozygote. However, two control subjects had repeated protein S levels at 0.50 U/mL, ie, were very likely heterozygotes. We therefore maintain that the possibility may not be completely ruled out that the previously reported findings from studies in selected groups are the result of cosegregating (unknown) additional genetic defects. On the other hand, it cannot be ruled out that our findings resulted in part from chance.

Our study was the first population-based and controlled study addressing this issue. For further clarity, we feel that there is a need for other controlled studies in unselected patient groups.

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REFERENCE

The accurate definition of protein S deficiency may avoid the misestimation of the frequency of this defect [letter; comment]

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