

Thromboembolism and Factor VII Defect

I have read with interest the short paper on thromboembolism and factor VII deficiency by *Shifter et al.* [8]. I think a few comments along the following lines, are indicated.

(1) It is surprising to see that no antithrombin III and protein C assays are included in the 'Results' section. In the past a few cases of factor VII defect and associated thromboembolism have been described without specifying the ATIII levels of the *propositi* [1, 7]. However, this is not suited nowadays because of the widespread availability of ATIII and protein C assays.

(2) The study of the husband of the *proposita* (fig. 1 of the paper in question) is imperative before drawing any conclusion about the genetics of the defect. The husband is probably heterozygous for the defect, but this has to be proven. On the basis of the prothrombin time results it is impossible to allocate with certainty the *propositi*. For example, human brain thromboplastin prothrombin time yielded values of 26-28 s indicating that all patients were similarly affected. The same was true for human brain thromboplastin. Are they all heterozygous?

(3) Finally, and more important, there are doubts about the type of factor VII defect being investigated. In table I it seems that ox brain thromboplastin prothrombin time is normal. If this is so, the patient is not a case of factor VII deficiency but a case of factor VII Padua defect [3]. In this variant in fact, the ox brain thromboplastin prothrombin time is normal. The patients in question, however, present another disturbing feature. If ox brain thromboplastin is normal and factor VII antigen is low, one has to conclude that such reduced level is 'hyperactive' with regard to ox brain thromboplastins. If an antigen of 20% (table I of the paper in question) is capable of yielding a normal level of factor VII activity, as demonstrated by the normal ox brain thromboplastin prothrombin time, it has to be concluded that such factor VII is about five times as active as normal factor VII - an astonishing observation, if confirmed. In view of the above, the thromboplastin used in the

factor VII assay should be specified. It is known in fact that in factor VII Padua defect, factor VII is normal if a bovine thromboplastin is used in the assay system [3].

All these observations are of paramount importance, and it is surprising to see that the reviewers have failed to raise these points. The role played by factor VII on hemostasis *in vivo* is a very important one. As often in blood coagulation, understanding of the mechanism involved may be derived from careful clinical observations. Several factor VII variants have already been described and have contributed considerably towards the elucidation of the subject [2-6]. Case reports on the subject should be welcome, providing they supply adequate information. As it is, the paper creates only a disturbing confusion.

References

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Prof. Antonio Girolami,
Second Chair of Medicine,
Institute of Medical Semeiotics,
Padua (Italy)

Reply:

We are grateful for the comments and think that these remarks will be of interest to us and to others.

As Prof. Girolami remarked, it is a short paper on factor VII deficiency, and therefore not all the determinations done on this family were included. We performed a large battery of tests including a coagulation screening with the quantitation of all the intrinsic and extrinsic plasma factors, a fibrinolytic screening with the determination of fibrinogen split products, plasminogen, SK complex, plasmin, thereafter the bleeding time, platelet count, and so on. All these tests included also the inhibitors of coagulation and fibrinolysis, especially the antithrombin which was done by two methods, a functional one using chromogenic substrate and an immunological one using RID plates.

In the paper, on page 61, we wrote that all the coagulation and fibrinolysis tests were within the normal range. The protein C was not included because the family was studied in 1981 when the commercially available kit was not on the market. We think that it would be interesting for us to study all the members of the family by this test as well.

In our study, 14 members of the family were studied, but table I represents only the results of those

members with pathological changes, as it is mentioned in the title of this table. The husband was included in the study, the results of his tests were found to be within the normal range, and he was not drawn on the family tree. The factor VII assay was done with human thromboplastin (Behringwerke).

In answer to the remark that it can be factor VII Padua defect, we thought so too, but we have neither experience with this variant, nor a control plasma from a family with factor VII Padua defect, so we concluded that what is important is to establish an accurate diagnosis of the deficiency, and especially the fact that a link was observed between this defect and the increased thrombotic tendency. The 'hyperactive' factor VII described by Prof. Girolami can be a possible explanation.

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Draga Creter, MSc,
Department of Hemostasis,
Hasharon Hospital,
Petah-Tiqva 49382 (Israel)