The Congenital Variants of the Prothrombin Complex Factors

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I have read with great interest the Editorial on 'Variants of Vitamin K Dependent Coagulation Factors' (Acta haemat. 62: 1, 1979).

I would like to add a few comments on factor VII, factor IX and factor X variants.

Factor VII variants. There is no doubt that factor VII Padua represents the first factor VII abnormality for which a peculiar activation pattern was surely demonstrated. The discrepancy between rabbit and ox brain thromboplastin clotting time is striking. However, I think factor VII Verona also represents a factor VII abnormality which justifies the toponym given to it. The reasons, part of which deal with still unpublished observations, are the following:

The two propositi are double hetero-zygotes for true factor VII deficiency and abnormal factor VII.

The factor VII levels in the two propositi are about 20% of normal with rabbit or human brain thromboplastins but about 40% with ox brain thromboplastins. This was not included in the original paper [4] since at that time we failed to recognize it. It was found subsequently, after the discovery of factor VII Padua, when additional tests were carried out. However, even in the original paper, it was shown that the thrombo-test was less prolonged than expected.

(3) Furthermore, factor VII Verona seems to be activated by exposure to glass and/or cold in an abnormally fast manner.

That the interaction between tissue thromboplastins, Ca^{++} and factor VII is much more complicated than was originally thought is well documented by another abnormality which recently came to our attention, factor VII Padua² [6]. This factor VII shows increased sensitivity to ox brain thromboplastins. Such thromboplastin seems to play a pivotal role in detecting factor VII abnormalities. In some cases, there is no sensitivity at all (Padua), in others, there is a partial sensitivity (Verona) and in still others, on the contrary, an exaggerated sensitivity (Padua²) to ox brain thromboplastin. Needless to say that many additional variants may exist. It is interesting to note that pig brain thromboplastins behave in a way similar to ox brain preparations [5, 6]. In the past, ox brain thromboplastin was claimed to be particularly sensitive to factor X and/or to the so-called, but never proven, coumarin-induced inhibitors [8]. Probably, the main peculiarity of this thromboplastin is its close and multifaceted relationship

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Table I. Main features of surely proven factor X variants

Index patient

Factor X activity

tissue RVV- cephalin

thromboplastin cephalin

Factor X Proposed

antigenomenclature

absent

Mr. Stuart (classical
absent
absent
factor X deficiency)

Miss Prower
low
low
Mrs. Minin
low
normal
(factor X Friuli)

X-
absent
low normal X+
low normal X Friuli

with factor VII, together with a marked sensitivity to the hemophilia B defect. Since all the families with the three defects studied by us live in the north-eastern part of Italy, namely in an area about the size of Holland, I suspect that the different abnormalities are just an expression of a closely related molecular change.

The following tentative classification for the factor VII defects may be proposed: (1) factor VII₋ (classical factor VII deficiency); (2) factor VII₊ (patients with low activity but normal CRM); (3) factor VII reduced (patients with low activity and variable CRM which, however, is always higher than the clotting counterpart but never normal); (4) factor VII Padua (rabbit brain); (5) factor VII Verona (rabbit and human brain); (6) factor VII Padua_< (ox brain).

Indication of the thromboplastin that yields the lowest factor VII activity level is absolutely necessary in cases with abnormal activation patterns, lest confusion is generated with simple factor VII₊ or factor VII reduced variants. It is interesting to note that variants with abnormal activation patterns had not been predicted in the genetic nomenclature proposed by Graham et al. [7].

Factor IX variants. The association of hemophilia B and mild factor VII deficiency should be kept in mind as a peculiar form of factor IX deficiency.

Factor X variants. The surely proven variants of factor X deficiency known today, are 3, namely Mr. Stuart, Miss Prower and Mrs. Minin (factor X Friuli). The main features of these 3 index patients are summarized in table I. As a matter of fact only the factor X Friuli deficiency satisfies the 'abnormal' activation requirement proposed in the Editorial.

In Miss Prower's deficiency there is no difference between RW-cephalin and tissue thromboplastin activation of factor X. The patient described by Denson et al. [1] as D.E.C. is a

factor X Friuli patient who was extensively reported by us [2]. A comment in this regard was already included in a previous paper [3]. The other cases reported by Denson et al. [1] represent cases of classical factor X deficiency (cases M. M., G. S., L. S.) or of factor X reduced (case R. E. D.). The latter could represent a 4th factor X variant.

The patient presented by Parkin et al. [9] in 1974 has received no confirmation and some doubts are justified since no spe-

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cific factor X assay was included in the study.

I fully agree with the recommendations to use several 'activating' systems in the investigation of congenital clotting defects. Unfortunately, the methods pertaining to Ca^{++} binding capacity, adsorption to phos-pholipids and proteolytic digestion are not widely known yet and are still in need of a satisfactory standardization.

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