Variants of Vitamin K Dependent Coagulation Factors

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Congenital disorders of blood coagulation can be due to the complete absence or decreased concentration of one of the coagulation factors or to the production of an abnormal one. The abnormal inactive coagulation factors are usually referred to as CRM-positive or CRM-reduced variants. CRM is an abbreviation for material that shows a cross-reaction with an antibody against a specific coagulation factor. True deficiencies as well as abnormal variants of the vitamin K dependent factors have been reported [1, 2, 6, 7]. Usually, the variants are detected by means of their reduced coagulant activity; the latter becomes apparent by comparison of the results of functional and immunological assays. The variants can be characterized further by biochemical methods and by their ability to be activated by nonphysiological agents like trypsin, sta-phylocoagulase, snake venoms and a number of thromboplastins. At the moment it appears that the severity of the bleeding symptoms only correlates with the residual coagulant activity.

The accompanying paper of Girolami et al [this issue] reports on the observation of a pedigree with a genetic variant of factor VII very similar to factor VII Padua. The factor VII Padua, described by the same authors [4], is the first genetic variant of factor VII of which the nature of the underlying defect might be hypothesized: it is highly probable that the mutation has occurred in that part of the molecule that is responsible for its interaction with the tissue factor. Apart from these two (possibly related) families eight other families have been reported to have a variant of factor VII with a strongly reduced coagulant activity.

At present we know 9 defective variants of factor II (Barcelona, Quick, Cardeza, San Juan, Brussels, Padua, Mouse, Madrid, Metz), 5 variants of factor X (Friuli a.o.), and a very large number of factor IX variants. During the last 2 years about 180 pedigrees with hemophilia B have been found to have an abnormal factor IX molecule (hemophilia B⁺, CRM-positive, CRM-reduced). Whether the properties of all these factor IX variants are different cannot be established at this moment. Because specific immunologic assays for factors II, VII, IX and X have become widely available, it can be expected that many additional variants will be detected in the near future.

At present detailed knowledge on the mechanism of action of the vitamin K de-

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pendent coagulation factors becomes available: the mechanism of proteolytic activation, the interaction with other coagulation factors (tissue factor, factor V, factor VIII), the binding of Ca^{2+} ions and the affinity for adsorption to phospholipid surfaces. This knowledge can now be used to develop simple assays for several functional aspects of these coagulation factors.

Communication on the subject of genetic variants presently is dependent on the use of geographical epitheta like prothrombin Barcelona, factor VII Padua, factor IX Chapel Hill or factor X Friuli. Such a nomenclature will be sufficient as long as the number of variants is relatively small, and their abnormality is clearly defined. However, when both the detection rate and the number of so-called CRM-positive variants increases, the need for a more adjusted nomenclature becomes apparent (factor VII and especially factor IX variants). In our opinion such a nomenclature should give information on the observed abnormalities of the variant molecule. As long as the only abnormality consists in a reduced specific coagulant activity there is no criterium to distinguish the variants from each other.

The majority of the factor II variants has been studied extensively and it appears that variants referred to by different names really represent different abnormal factor II molecules. Most of the variants of factor VII have not been characterized and we consider it appropriate that they have not been given names. However, in our opinion, the introduction of factor VII Verona is not justified. In contrast to factor VII Padua, factor VII Verona [3] cannot be distinguished by any technic from the other factor VII variants with low specific coagulant activity. A reversed situation exists in the field of factor X. The 3 variants described by Denson et al. [2] in 1970 are clearly different from each other although their characterization might be extended. In our opinion these variants are entitled to have a name. As might be expected some superfluous name giving has started in the field of factor IX variants where, for instance, factor IX Worcester [8] stands for a factor IX molecule without detectable coagulant activity. The factor VII variant introduced as factor VII Padua [4] gives an excellent example of how a very simple experiment (one prothrombin time with a human thromboplastin and one prothrombin time with a bovine thromboplastin) can give valuable information on the nature of the defect. Other tests of comparable simplicity – providing information on for instance Ca^{2+} binding capacity, affinity for adsorption to phospholipids, or susceptibility to proteolytic activation – may be developed and included in the routine screening of coagulation factor variants. It is our proposal that the results of such assays are used as basis for an appropriate nomenclature. Such a nomenclature can be developed using the initial proposals of the Working Party of Graham et al. [5].

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