Dear Sir,

The contact phase of blood coagulation is composed of three clotting proteins, namely FXII or Hageman Factor, Prekallikrein (PK) and High Molecular Weight Kininogen (HMWK) [1]. Since patients with a deficiency of any of these proteins do not show a bleeding tendency, the defects have been often disregarded or under evaluated.

However, this contact phase of blood coagulation has received new attention in recent years.

A body of experimental studies in knockout animals, usually mice, suggest that the contact phase of blood coagulation plays a role in the development and progression of experimentally induced thrombosis [2-5].

Knockout mice are reported to protect against thrombosis. This has stimulated the possibility that anti contact phase drugs could find a therapeutic use in humans since the inhibitory effect would not cause bleeding. In fact, since congenital FXII and PK deficiency are not associated with bleeding, there would be no danger of interfering with the normal hemostatic function.

These observations are in sharp contrast with clinical observations that congenital deficiencies of these factors, present thrombotic events or, better, do not protect from thrombotic events. These thrombotic events seem particularly frequent, in PK deficiency that is also often associated with hypertension [6-9].

The conundrum is unresolved due to the fact that there is no controlled longitudinal study on the incidence of thrombosis in all these patients.

The only studies available concern FXII deficiency and showed that there is no difference in the incidence of venous or arterial thrombosis in patients with congenital severe (1% of normal) or mild (about 50% of normal) FXII deficiency as compared with unaffected family members [10,11].

No similar study is available for PR kallikrein (PK) deficiency or High Molecular Weight Kininogen (HMWK) deficiency.

However, several observations and case series studies indicate that hypertension and its related complications (MI and stroke) seem fairly common in PK deficiency [8,9].

Thrombotic events have been reported even in HMWK deficiency, but the observations are too few to have relevance [1,12].

There is another peculiar observation with regard to PK deficiency: the large majority of thrombotic events concern the arterial system. As the matter of fact, the only venous thrombosis occurred in two sisters who, besides PK deficiency, showed also severe obesity [13].

On the contrary, these is no similar striking difference in FXII deficiency. It seems, in other words, that arterial thrombosis is probably associated with PK deficiency. This action seems mediated by the hypertension which has been frequently found in patients with PK deficiency [6].

Another peculiar fact concerns the observation that African Americans are frequently affected by PK deficiency [6]. It is known that these patients present often hypertension and its complications. The presence of the PK defect could play a role in the known increased mortality rate due to cardiovascular diseases seen among African Americans [14-17].

There is a need to clarify the matter. The only solution is a long-term study with the enrollment of enough patients in comparison with unaffected family members as recently done for FXII deficiency. The major drawback for this type of study is represented 1) by the fact that these patients are usually asymptomatic and therefore often unrecognized; 2) no center has by itself the possibility to accumulate a sufficient number of patients.

It is therefore inevitable a joint effort of several countries and the organization of a steering committee.

Since several animals with congenital PK deficiency have been described, a long-term study in some of these animals (dogs) could also be useful [17].

Due to the heavy cost to society of hypertension and its complications any cost should be faced and accepted.

The problem has been synthesized in the phrase “no contact, no thrombosis” [18]. We think it is safer to state for FXII deficiency “no contact and thrombosis as usual”. However, the statement for PK deficiency has probably to be changed in "no contact and more thrombosis" [19]. These considerations are based on extensive clinical studies [8,10,19] and are the only important for clinicians.

Finally, we have some doubts about the possibility of hemostasis since, if the contact phase is blocked, there may be a defective or impaired activation and function of FXI and FXI deficient patients do bleed [20].

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