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Case Report

Combined Factor V and Factor VII Deficiency Due to an Independent Segregation of the Two Defects

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SUMMARY: A patient with combined factor V and factor VII deficiency is described together with a family study. The propositus appeared to be double heterozygous for factor V and factor VII deficiency. Since the patient showed a parallel decrease of activity and antigen, he appeared to be double heterozygous for a true deficiency. The patient had inherited the factor V defect from the mother and the factor VII defect from the father. The parents of the propositus were not consanguineous. Other family members were found to have isolated factor V or factor VII deficiency. This is the third family so far described with this peculiar combined defect but the first to be investigated by clotting and immunologic assays. **Key Words:** Factor V deficiency—Factor VII deficiency—Combined defect.

Partial deficiencies at a heterozygous level of a single coagulation factor, for example factor VII, are common but most of them may go undetected since patients are asymptomatic (1). They are often incidentally discovered during preoperative screening. Patients with a combined deficiency of two factors are less common; cases of combined factors V and VIII, or VII and VIII, or factor VII and factor IX deficiencies have been reported (2–6). The association between factor V and factor VII is extremely rare. As yet, only two families of a combined factor V and factor VII deficiency have been described in the literature (7,8). However, neither of the two families were investigated from an immunologic viewpoint.

This article presents another family with this peculiar defect whose members have been investigated from a clotting and an immunologic viewpoint.

CASE REPORT

A 13-year-old boy was sent to us in October 1997 because he bled profusely after adenoidectomy. During infancy the patient presented with no important bleeding manifestations. He had only occasional epistaxis. The parents were not consanguineous. The patient's mother and one sister had minor epistaxis while the patient's father and one brother were asymptomatic. The family history is shown in Fig. 1.

MATERIAL AND METHODS

Prothrombin time (PT) and partial thromboplastin time (PTT) were performed according to standard procedures. Factor VII activity was determined in a Heller coagulometer (San Mateo, CA, U.S.A.) using human placenta thromboplastin (Thromborel, Behringwerke AG, Marburg, Germany). The substrated used was an equal parts mixture of factor VII-deficient plasma and adsorbed normal plasma (9). Factor VII antigen was measured by an enzyme-linked immunosorbent assay (ELISA) using the reagents supplied by Diagnostica Stago Laboratories, Asnieres-Sur-Seine, France.

Factor V clotting activity was carried out as previously reported using a congenitally deficient plasma as substrate and a human placenta derived thromboplastin. Factor V antigen evaluation was performed by an ELISA method as previously reported (10).

RESULTS

The results of the coagulation tests are shown in Table 1. The propositus had a mild prolongation of the PT. Factor VII activity and antigen was 60% and 66% of normal, respectively. Factor V activity and antigen was 65% and 70% of normal, respectively. All the other clotting factors were within normal limits. He was consid-

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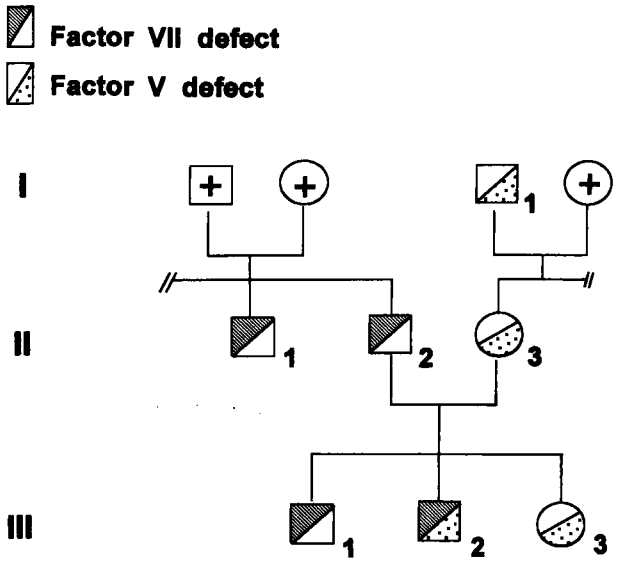

FIG. 1. Family history. The propositus is III_2. The two defects segregate separately.

ered to be double heterozygous for factor VII and factor V true deficiency.

One uncle on the paternal side, the father, and the brother showed a slight factor VII deficiency. The maternal grandfather, the mother, and the sister had a slight factor V deficiency. In all instances there was a good correlation exhibited between clotting and immunologic assays. These were considered subjects to be heterozygous for true deficiency for factor VII and factor V, respectively (Table 2).

In addition, all these patients showed a 1- to 2-second prolongation of the PT. No liver disease was present in the family members investigated and consistent results were found on repeated clotting and immunologic assays carried out during the 18-month period.

DISCUSSION

Congenital factor VII deficiency and parahemophilia are still considered rare coagulation disorders (7,8). Factor VII deficiency seems to occur more frequently than factor V deficiency (9,11,12). Due to this higher prevalence it is not surprising that factor VII deficiency or abnormality has been described in association with several other congenital clotting defects such as hemophilia A, hemophilia B, and Von Willebrand disease (2–6,13). On the contrary, factor V deficiency has been rarely associated with other clotting factors, with the exception of factor VIII to give the combined factor V and factor VIII deficiency (14,15). Two types of this peculiar disorder have been known to exist, namely type I in which there is a causal association between factor V true deficiency and hemophilia A and type II, which is caused by a common defect in the synthesis of factor V and VIII. This second type has been recently demonstrated to be due to a defective gene located in the long arm of chromosome 18. The defective gene causes a mutation in an endoplasmatic reticulum-Golgi apparatus intermediate compartment protein (16).

The first type is less frequent, there is no consanguinity between the parents, and factor V is about 50% of normal (heterozygous) whereas factor VIII is considerably lower (1–5%). On the contrary, type I (II) disease is characterized by a parallel decrease in factor V and factor VIII activities and by the frequent consanguinity between the parents.

A limited number of cases of other combined coagulation factors deficiencies have been reported in the lit-

TABLE 1. *Coagulation findings in the propositus*

		Normal values
Bleeding time	2 minutes 20 seconds	<4 minutes
Platelet count	308×10^9/L	$150–350 \times 10^9$/L
PT (s)	18.6	14–16
PTT (s)	39.6	30–40
Fibrinogen (g/L)	1.69	1.5–3.5
Factor V act. (%)	65	80–120
Factor V ag. (%)	70	80–120
Factor VII act. (%)	60	80–120
Factor VII ag. (%)	66	80–120
Factor X act. (%)	80	80–120
Factor VIII:C (%)	80	60–160
vWF:Ag (%)	92	60–160
vWF:RCof (%)	83	60–130

PT, prothrombin time; PTT, partial thromboplastin time; act., activity; ag., antigen; vWF, Von Willebrand factor.

TABLE 2. *Main clotting and immunologic assay in the family members investigated*

	PT (s)	PTT (s)	Factor V activity (%)	Factor V antigen (%)	Factor VII activity (%)	Factor VII antigen (%)
III-2 Propositus	18.6	39.6	65	70	60	66
III-1 Brother	**16.5**	**36.6**	**82**	76	74	**76**
III-3 Sister	**17.1**	**38.4**	**62**	69	96	**85**
II-2 Father	**15.6**	**34.0**	**94**	83	73	**76**
II-3 Mother	**16.0**	**42.0**	**52**	65	100	**100**
II-1 Paternal uncle	15.3	33.9	120	110	78	**75**
I-1 Maternal grandfather	16.6	43.0	65	66	105	**100**
Normal Values	13–14	30–40	80–120	80–120	80–120	80–120

PT, prothrombin time; PTT, partial thromboplastin time.

erature (2–6,13). Only two families of combined factor VII and factor V coagulation defect are described (7,8). Patients with factor VII deficiency at the heterozygous state are usually asymptomatic or may have a mild or doubtful hemorrhagic tendency only in a few cases (9, 11,12). Patients heterozygous for factor V deficiency are also often asymptomatic. The severity of bleeding symptoms does not always correlate well with plasma factor V levels. It seems that the association of combined factor V and factor VII defect at a heterozygous state does increase the severity of the bleeding manifestation. In fact, the propositus was more symptomatic than patients heterozygous for factor V or factor VII isolated deficiencies.

The association of different clotting defects may be, in general, of two types. It may be the result of an independent segregation of two defects in the same family or it may be secondary to a common gene(s) malfunction. Since no relation has ever been demonstrated between factor V and factor VII it is sure that the present family belonged to type I. This is also fully consistent with the hereditary pattern and the independent segregation of the two defects.

This case is a typical example of combined association of two distinct defects (type I). The two defects are examples of "true" deficiencies since there was no discrepancy between clotting and immunological assays.

The presence of a clotting defect in this family was detected only when the propositus became symptomatic. In the past no attention was given to a mild prolongation of the PT and PTT of the mother and maternal grandfather.

Factor VII deficiency, factor V deficiency, and combined factor V and factor VII deficiency at the heterozygous state are probably more frequent and underestimated in the population than reported in the literature. This article has a practical implication for all physicians and technicians involved in coagulation studies. A persistent, even if mild, prolongation of PT and/or of the PTT requires a complete coagulation study particularly if the propositi are symptomatic. The study has to include the specifics of clotting and immunologic assays of factors known to affect the global tests.

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