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A Japanese Family of Hereditary Deficiency of Plasma Thromboplastin Antecedent(Factor XI)

*Kenji Shinohara, Yasuko Konishi, Yoichi Azuno, Katsunori Yamada, Hiroko Sasaki, Toshio Kaneko and Noboru Matsumoto**

Third Department of Internal Medicine, Yamaguchi University School of Medicne, and *The School of Allied Health Sciences, Yamaguchi University, Ube, Yamaguchi 755, Japan

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Abstract A Japanese family of hereditary deficiency of plasma thromboplastin antecedent (PTA, factor XI) was reported. The parents of the propositus were of consanguinous marriage. The levels of plasma factor XI activity and antigen of the homozygotes were less than 1% of normal, and those of heterozygotes were approximately half of normal. The deficiency was transmitted as autosomal recessive trait. The homozygotes had no episodes of troublesome bleedings. The platelets of the propositus contained intrinsic factor XI-like activity as in normal, and the compensatory role of platelet factor XI-like activity for the initiation of the intrinsic pathway of coagulation was suggested.

*Key Words:*hereditary deficiency of PTA, platelet factor XI-like activity

Introduction

Hereditary deficiency of plasma thromboplastin antecedent (PTA, factor XI) is a rare disorder associated with a mild bleeding tendency[1-7]. Since the original report by Rosenthal and Dreskin[1], several hundread cases had been reported[1-7]. The disease had been reported almost exclusively in the Jewish families[2], but had been reported also in the different parts of the world[3-7]. In Japan, the disease is extremely rare and more than twenty families had been reported[6-7]. However, only a few homozygotes had been identified by measuring the levels of factor XI activity and antigen in the plasma[6-7].

The homozygotes had only mild episodes of bleeding, despite the markedly reduced plasma factor XI activity[1-7].

We report a Japanese family of hereditary deficiency of plasma factor XI, and a possible compensatory role of platelet factor XI-like activity in the hemostatic mechanism for the deficient plasma factor XI activity was discussed.

Case

A 43 years old Japanese female was

incidentally found to have prolonged aPTT during the preoperative studies for uterine myoma. She had no underlying diseases, nor used any speeial drugs. She had not received major surgery, nor had any episodes of troublesome bleeding.

Materials and methods

Citrated plasma samples were prepared from blood to which one-tenth volume of 3.8% sodium citrate was added.

Functional activities of individual clotting factors were assayed by a modified PTT, using factor deficient plasma samples as substrate.

Plasma thromboplastin antecedent (factor XI) antigen was estimated by radioimmunoassay[8].

Preparation of washed platelets were done by albumin gradient separation and washing[9].

Other laboratory values were obtained by using routine methods available at university hospital and Special Reference Laboratory (Tokyo, Japan).

Results

Fig. 1 shows the family pedigree. Father (I-1), and grandmother of mother (I-2) were cousins.

Hemostatic studies of the propositus (II-2) are shown in Table 1 She had markedly prolonged aPTT, which was corrected by normal plasma, normal serum, and only partially by absorbed plasma. The levels of plasma factor XI activity and antigen were markedly reduced to less than 1% of normal (Table 2). There was no circulating inhibitor against factor XI activity. Physiologic inhibitors of factor XI, such as antithrombin III, α-1-antitrypsin, C-1′-inactivator, α-2-macroglobulin, α-2-antiplasmin were normally present. The factors of plasma kinin system, prekallikrein, high molecular weight kininogen and factor XII were normally present (Table 1).

The levels of plasma factor XI activity and antigen of the parents were approximately half of normal and were heterozygotes. Among the siblings, besides the propositus, other two members (II-5, -6) were homozy-

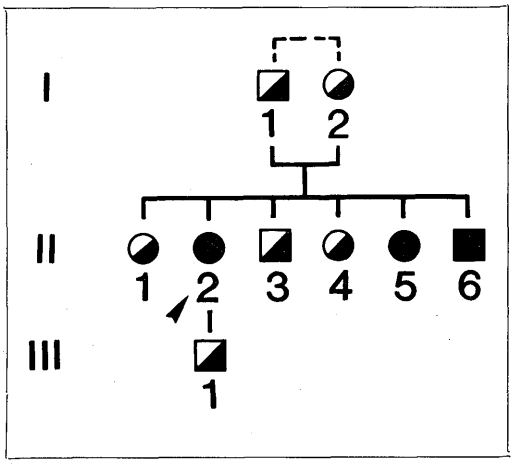

Fig. 1 The family pedigree.
□ Male
○ Female
■● Homozygote
◪◔ Heterozygote
◢ Propositus

Table 1 Hemostatic studies of the propositus.
( ): normal value or normal control

platelets	19.8×10⁴/mm³
bleeding time	2.5 min
PPT	11.0 sec (11.2)
aPTT	74.6 sec (24.6)
normal+patient	35.0 sec
normal serum+patient	26.5 sec
normal, adsorbed+patient	52.4 sec
capillary fragility test	numerous
clot retraction (FV%)	23% (0-20)
clotting time	
glass	27.0 min(8-12)
silicon glass	56.0 min(36.0)
Factor VIII	100%(80-120)
IX	74%(80-120)
X	100%(80-120)
XI	<1%(80-120)
XII	59%(80-125)
prekallikrein	106%(80-125)
high molecular weight kininogen	107%(63-146)
antithrombin III	114%(82-132)
α-1-antitrypsin	231mg/dl(196-326)
C-1′-inactivator	41mg/dl (15-35)
α-2-macroglobulin	227mg/dl(114-276)
α-2-antitrypsin	117%(85-115)

gotes, and other three members(Ⅱ-1, -3, -4) were heterozygotes. A child of the propositus (Ⅲ-1) was heterozygote (Figure 1 and Table 2).

Washed platelets of the propositus were suspended in her own plasma (platelet count of approximately $20\times10^4/mm^3$), and were lyzed by repeated freeze and thaw, and the lysate was assayed for aPTT. The addition of the lysate of the patient's platelets shortened aPTT of the patient's plasma as in normal platelets (Table 3).

Table 2 Levels of factor Ⅺ activity and antigen of the family members.

Kindred Member	Factor Ⅺ	
	Activity (%)	Antigen (%)
Ⅰ-1	46	21
Ⅰ-2	56	26
Ⅱ-1	56	38
Ⅱ-2	1	1
Ⅱ-3	78	50
Ⅱ-4	52	34
Ⅱ-5	1	1
Ⅱ-6	1	1
Ⅲ-1	52	64
Normal Range	80-120	59-159
		(54.69)#

( )#: values of normal control measured simultaneously with the patients.

Table 3 The aPTT in the presence of the lysate of the platelets.

combinatfon	aPTT(sec)
1. patient's platelets+patient's plasma	51
2. normal platelets+patient's plasma	55
3. patient's plasma alone	77

Discussion

The mode of inheritance of factor Ⅺ deficiency had been disputed[10-11]. However the bulk of the data suggested that it was, transmitted as autosomal recessive trait[11], and our family study was consistent with the mode of inheritance.

The deficiency results from the impaired synthesis of the molecule of factor Ⅺ[5-8,12-13], Our family study supports the fact and the homozygotes had markedly reduced amounts of factor Ⅺ antigen and the heterozygotes had variable amounts of antigen of approximately half of normal. The amounts of functional activity change parallel with the amounts of antigen. However, the severiety of bleeding could not be correlated with the level of factor Ⅺ acivity or antigen [12-13], and most of the reported homozygotes suffered from very mild episodes of bleeding despite the markedly reduced plasma factor Ⅺ activity[1-7].

Human platelets can participate in the interaction of early phase of intrinsic coagulation proteins, including those of "contact phase", i.e. factor Ⅻ, prekallikrein, high molecular weight kininogen and factor Ⅺ[14-15], and in our case, those were normally present except for factor Ⅺ.

Washed platelets by albumin density gradient procedure contain less than 0.2% of plasma factor Ⅺ activity[15], and contain intrinsic factor Ⅺ-like activity in the membrane which molecule is immunologically related but is structurally distinct from plasma factor Ⅺ[14-17].

The mild episodes of bleeding in the homozygotes, and the shortened aPTT of the patient's plasma in the presence of the lysate of the patient's platelets, support the evidence that the platelet factor Ⅺ-like activity can participate in contact activation for the initiation of the intrinsic coagulation which operates in the absence of plasma factor Ⅺ[14),17] It is also suggested that the syntheses of the molecules of plasma factor Ⅺ and platelet factor Ⅺ-like activity are genetically determined independently[15),17].

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References

1) Rosenthal, R.L., Dreskin, O.H. and Rosenthal, N.: New hemophilia-like disease caused by deficiency of a third plasma thromboplastin factor. *Proc. Soc. Exp. Biol. Med.*, 82 : 171-174, 1953.

2) Seligsohn, U.: High gene frequency of factor XI (PTA) deficiency in Ashkenazi Jews. *Blood* ,51 : 1223-1228, 1978.

3) Zacharski, L.R. and French, E.E.: Factor XI (PTA) deficiency in an English-American kindred. *Thromb. Haemost.*, 39 : 215-222, 1978.

4) Niskanen, E.O., Saito, H. and Cline, M.J.: Plasma thromboplastin antecedent (factor XI) deficiency in a black family. *Arch. Intern. Med.*, 141 : 936-937, 1981.

5) Aghai, E., Yaniv, I. and David, M.: Factor XI deficiency in an arab moslem family in Israel. *Scand. J. Haematol.*, 32 : 327-331, 1984.

6) Mukaiyama, H. and Tsukimoto, I.: Four cases of one family with congenital factor XI (plasma thromboplastin antecedent) deficiency. *Jpn. J. Clin. Hematol.*, 21 : 1877-1884, 1980.

7) Kuzumi, S., Takamatsu, Y., Ishida, Y., Takata, N., Fujimura, K., Kuramoto, A., Koganemaru, S. and Saito, H.: A study on platelet factor XI-like activity in a family with congenital factor XI deficiency. *Jpn. J. Clin. Hematol.*, 25 : 1313-1319, 1984.

8) Saito, H. and Goldsmith, G.H. Jr.: Plasma thromboplastin antecedent (PTA, factor XI): A specific and sensitive radioimmunoassay. *Blood*, 50 : 377-385, 1977.

9) Walsh, P.N.: Albumin density gradient separation and washing of platelets and the study of platelet coagulant activities. *Br. J. Haematol.*, 22 : 205-217, 1972.

10) Rapaport, S.I., Proctor, R.R., Patch, M.J. and Yettra, M.: The mode of inheritance of PTA deficiency: Evidence for the existence of major PTA deficiency and minor PTA deficiency. *Blood*, 18 : 149-165, 1961.

11) Muir, W.A. and Ratnoff, O.D.: The prevalence of plasma thromboplastin antecedent (PTA, factor XI) deficiency. *Blood*, 44 : 569-570, 1974.

12) Forbes, C.D. and Ratnoff, O.D.: Studies on plasma thromboplastin antecedent (factor XI), PTA deficiency and inhibition of PTA by plasma: Pharmacologic inhibitors and specific antiserum. *J. Lab. Clin. Med.*, 79 : 113-127, 1972.

13) Rimon, A., Schiffman, S. Feinstein, D.I. and Rapaport, S.I.: Factor XI activity and factor XI antigen in homozygous and heterozygous factor XI deficiency. *Blood*, 48 : 165-174, 1976.

14) Walsh, P.N. and Griffin, J.H.: Contributions of human platelets to the proteolytic activation of blood coagulation factors XII and XI. *Blood*, 57: 106-118, 1981.

15) Tuszynski, G.P., Bevacqua, S.J., Schmaier, A. H., Colman, R.W. and Walsh, P.N.: Factor XI antigen and activity in human platelets. *Blood*, 59 : 1148-1156, 1982.

16) Schiffman, S., Rimon, A. and Rapaport, S.I.: Factor XI and platelets; evidence that platelets contain only minimal factor XI activity and antigen. *Br. J. Haematol.*, 35 : 429-436, 1977.

17) Lipscomb, M.S. and Walsh, P.N.: Human platelets and factor XI; localization in platelet membranes of factor XI-like activity and its functional distinction from plasma factor XI. *J. Clin. Invest.*, 63 : 1006-1014, 1979.