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An isolated factor V deficiency (Parahemophilia): a case report

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This is a case report of an isolated factor V deficiency which is very rare. Only 150 cases were reported over a period of 48 years and it has never previously been reported in Thailand. Factor V is an essential enzyme important for the coagulation process. Deficiency of factor V causes prolongation of both prothrombin time (PT) and activated partial thromboplastin time (APTT). However, the factor V deficient patient usually shows mild clinical bleeding e.g. ecchymosis, epistaxis, oral hemorrhage upon and post-dental extraction. The bleeding problem can be easily controlled with transfusion of fresh frozen plasma (FFP) or fresh whole blood (FWB). The specific factor V assay of our patient, his father and mother were 2, 41 and 47% of normal respectively. This is thought to be a case of congenital factor V deficiency which was transmitted in an autosomal recessive manner. Although deficiency of factor V and VIII are often found together, this patient had normal levels of factor VIII. The abnormality at the molecular level will be the further studied.

Key words: *Factor V deficiency, Parahemophilia.*

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อรัญญา กิตติกัลยาวงศ์, ฉวีวรรณ อัมพันธ์, ปัญญา เสกสรรค์. รายงานผู้ป่วยขาดแฟคเตอร์ V (พาราฮีโมฟีเลีย) 1 ราย. จุฬาลงกรณ์เวชสาร 2540 เม.ย;41(4): 287-95

ได้รายงานผู้ป่วย 1 ราย มีการขาดแฟคเตอร์ V เพียงอย่างเดียว ซึ่งพบได้น้อยมาก มีรายงานเพียง 150 ราย ใน 48 ปี ในประเทศไทยยังไม่เคยมีรายงานเลย แฟคเตอร์ V เป็นเอนไซม์ที่สำคัญจำเป็นสำหรับขบวนการแข็งตัวของเลือด การขาดแฟคเตอร์ V ทำให้ผลการตรวจ prothrombin time (PT) และ activated partial thromboplastin time (APTT) ยาวผิดปกติ แต่อย่างไรก็ตามคนไข้จะมีอาการไม่รุนแรงมักจะมีจ้ำเลือด เลือดกำเดาไหล มีเลือดออกในช่องปาก และหลังถอนฟัน การรักษาทำได้ง่าย โดยการให้ fresh frozen plasma (FFP) หรือ fresh whole blood (FWB) ระดับแฟคเตอร์ V ในคนไข้, พ่อ และ แม่ เป็น 2, 41 และ 47% ตามลำดับ คนไข้ครอบครัวนี้จัดเป็นคนไข้ขาดแฟคเตอร์ V ที่มีการถ่ายทอดแบบ Autosomal recessive แม้จะมีรายงานว่ามักพบการขาดแฟคเตอร์ V ร่วมกับการขาดแฟคเตอร์ VIII บ่อย ๆ แต่คนไข้รายนี้มีระดับแฟคเตอร์ VIII เป็นปกติ รายงานผู้ป่วยนี้เป็นการรายงานผู้ป่วยที่ขาดแฟคเตอร์ V โดยไม่มีการขาดแฟคเตอร์ VIII ร่วมด้วย การตรวจความผิดปกติในระดับโมเลกุลจะได้ทำการศึกษาต่อไป

Factor V deficiency, or parahemophilia as termed by Owren, is very rare; only about 150 cases were reported over a period of 48 years.⁽¹⁾ Our institute, Chulalongkorn Memorial Hospital, is one of the referral centers for other hospitals in Thailand. Patients with hematologic problems are referred to our hematology unit for diagnosis and treatment.

We describe here a patient referred from Sanamchan Hospital whose presenting symptoms were ecchymosis and prolonged bleeding after dental extraction. The diagnosis was isolated as factor V deficiency. This is the first case report of this type of hemostatic defect in our institute and also the first in Thailand. A review of factor V and factor V deficiency is presented. The methods for the investigation of this defective hemostasis are also briefly described here.

Case report

The patient was a 3 year-old Thai boy who came to our attention because of a bleeding problem after dental extraction. His past history showed mild bleeding manifestations of easy bruising, ecchymosis and mild bleeding from the gum one week before admission. He had had an accident cawing his lip to be injured and there was bleeding from a laceration of gum around a tooth. Dental extraction at Sanamchan Hospital caused a persistent bleeding problem. He was referred to Chulalongkorn Memorial Hospital on February 1, 1996 after 4 days of bleeding.

On initial examination the patient looked pale, but without icteric sclera. The pulse rate was 140/minute, regular full and his blood pressure was 90/40 mmHg. He had bleeding from the gum around the area of dental extraction. The chest was clear. The heart was normal S_1 , S_2 with and no murmur. His abdomen was soft and not distended. The liver and spleen examinations were negative. No joint deformity was noted. His skin showed ecchymosis at the forearms and legs.

Laboratory investigations revealed the following: CBC were Hct 17%, wbc $8500/\text{mm}^3$, platelet $193,000/\text{mm}^3$, WBC differential: Neutrophil 64%, Lymphocyte 44%. Monocyte 2% NRBC 2/100 wbc. and Prothrombin time (PT) was 47.3 seconds (control 13.0 seconds). Activated partial thromboplastin time (APTT) was 92.4 seconds (control 30.1 seconds). Bleeding time was 4 minutes. Therapy was initiated with gauze and adrenaline pack to stop the bleeding. Transamin at a dosage of 250 mg was administered every 6 hours. Transfusion of fresh frozen plasma (FFP) to supply coagulation factors was given.

The patient improved after transfusion of the FFP and was discharged after 1 week. He was followed up periodically and multiple hematological evaluations were performed to elucidate the real defect of his bleeding tendency.

Periodic hematological investigation results are shown in Table 1. The results revealed prolongation of venous blood clotting time (VCT) as well as PT and APTT, but normal thrombin time (TT). A correction study with his blood mixed with normal plasma showed that his PT and APTT became normal and this indicated the coagulation factor deficiency, not the inhibitor. Combined prolongation of PT and APTT may be the result of a defect at a common pathway or a defect at both extrinsic and intrinsic pathways. The coagulation factors which can be more easily detected are factor I (fibrinogen) and factor II (prothrombin). This patient had a normal level of about 400 mg/100 ml of fibrinogen, which correlated with his normal thrombin time (TT). Investigation of a defect in factor II could be done by examining the PT after adding the patient's plasma with substrate factor II deficient plasma (Owren's method). There was correction, so the patient had no defect in factor II. While waiting for substrate factor V and X deficient plasma from a commercial source, we investigated deficiency in factors of the intrinsic pathway as these which are more common in bleeding tendencies. Correction studies were done by mixing the patients's plasma with substrate factor VIII and

substrate factor IX deficient plasma and examining APTT. There were also corrections in this test, so that the patient had no defect in factors VIII and IX. There was also correction for factor VII identification, and the specific assay was 94% of normal. From these results, the defect was narrowed to two factors in the common pathway; factor V and X. Factor X was assayed and found 97% of normal. A correction study of factor V by examining PT after adding the patient's plasma with substrate factor V deficient plasma showed no correction. Factor V was assayed and found markedly decreased to only 2-5% of normal. Because deficiency of factor V and VIII are often found together a specific factor VIII assay was performed. The result showed 70-75% of normal. This is the case report of an isolated factor V deficiency, not factor VIII combination deficiency.

In Table II, results obtained for both father and mother are included. The specific factor V and VIII assays of the father were 41 and 54% respectively, and they were 47 and 76% for his mother. The results were suggestive of carrier states. The family pedigree, presented in Figure 1, showed no consanguineous marriage.

Table 1. Periodical Physical and Hematological Examinations.

	5 Feb 1996	18 Mar 1996	25 Mar 1996	25 Oct 1996	31 Oct 1996	18 Nov 1996	4 Feb 1997	11 Apr 1997
VCT (min)	30'	50'	-	-	-	-	40'	-
PT (Patient/control sec)	33.8/12.3	37.5/13.1	54.5/15.0	40.0/13.4	29.3/13.2	38.4/13.5	46.3/13.3	42.1/13.7
Correction study	16.0/12.3	-	-	16.2/13.4	-	14.7/13.5	-	-
APTT(Patient/control sec)	92.9/39.7	93.8/28.0	162.5/38.3	>4'/33.6	>4'/34.2	>4'/33.1	6'/33.9	4'50/32.0
Correction study	48.6/39.7	-	-	50.13.4	-	42.2/33.1	-	-
TT(Patient/control sec)	14.0/13.1	14.0/16.0	17.4/16.4	-	-	-	-	-
Fibrinogen level (mg/100 ml)	-	-	-	379/317	-	463/337	440/318	340/259
PT (Owren's)	-	21.4/21.0	-	-	-	-	-	-
(Factor II Screening)								
APTT (Mixed with Factor VIII def plasma)	51.0/39.7	-	-	-	-	55.9/33.1	-	-
(Factor IX def plasma)								
APTT (Mixed with Factor IX def plasma)	53.3/39.7	-	-	-	-	-	-	-
(Factor VII def plasma)								
PT (Mixed with Factor VII def plasma)	-	-	-	-	17.6/13.2	-	-	-
Factor VII assay	-	-	-	94 %	-	-	-	-
Factor X assay	-	-	-	97 %	-	-	-	-
(Factor V def plasma)								
PT (Mixed with Factor V def plasma)	-	-	-	-	49.5/13.2	42.6/13.5	-	-
Factor V assay	-	-	-	-	5 %	-	3 %	2 %
Factor VIII assay	-	-	-	-	-	75 %	70 %	73 %

Table 2. Hematological examinations of the patient's parents.

Lab investigations	Father	Mother
VCT (min)	8	11
PT (case/control sec)	17.5/13.7	14.2/13.7
APTT (case/control sec)	43.1/32.0	37.0/32.0
Fibrinogen level (mg/100 ml)	297/259	258/259
F V assay	41%	47%
F VIII assay	54%	76%

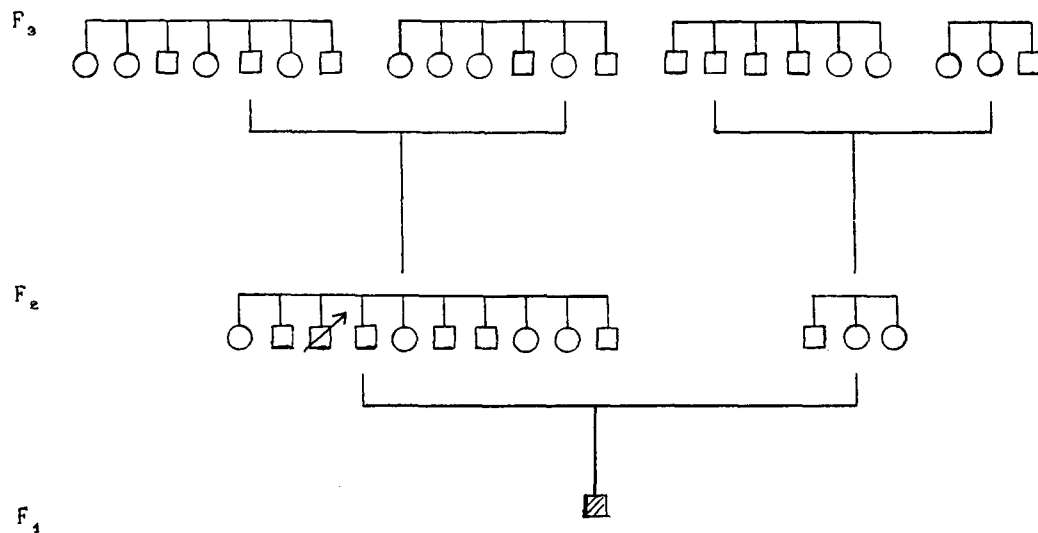


Figure 1. Pedigree of factor V deficient patient.

Discussion

Factor V is an essential enzyme catalysing the process of thrombin generation. Factor Va, the two subunit proteins produced by thrombin activation of factor V, performs its cofactor role in part by binding to the platelet membrane and functioning as the membrane receptor for factor Xa and appears to participate in the binding of prothrombin to the enzymatic complex. Deletion of factor Va from the prothrombinase complex decreases the rate of thrombin generation and shows some clotting alteration.

Factor V deficiency or parahemophilia is very rare and is usually not detected due to the mildness of the clinical picture. Such a diagnosis is not established until relatively late age in some patients. Age of onset of hemorrhagic syndromes

and diagnosis of factor V deficiency are mainly in the childhood (48%) and infancy (19%) periods. The sex ratio is equal. The types of hemorrhagic manifestations occurring with factor V deficiency are ecchymosis, epistaxis, oral hemorrhage and post dental extraction problems etc.⁽²⁾ These problems can be easily control controlled with transfusion of fresh frozen plasma (FFP) or fresh whole blood (FWB).^(2,3) Although the hemorrhagic symptoms are comparatively mild,⁽²⁻⁵⁾ severe bleeding and death have been reported.^(1,3,6-10) These severity may be due to other associated factors such as combination of factor VIII and/or von Willebrand factor (vWF) deficiency,^(9,11-17,21) defect of platelet factor V⁽⁷⁾ or inhibitors to factor V.⁽¹⁰⁾ There are as many cases of combined deficiency of both factor V and VIII as of only

single factor V deficiency.^(1,3-11,17-21) Congenital factor V deficiency is inherited as an autosomal recessive.^(2,3,6,9,20)

The methods for the investigation of this defective hemostasis are briefly described here. PT is used to demonstrate deficiencies of factors of the extrinsic system; i.e factors I, II, V, VII and X and the presence of inhibitors. APTT is used to demonstrate deficiencies of factors of the intrinsic system and the presence of inhibitors. TT is a rapid screening test for the conversion of fibrinogen to fibrin. Correction studies usually take the form of the addition to the test plasma of a small proportion of normal plasma fraction or serum. The pattern of correction of the prolonged PT or APTT can clearly identify factor deficiency or inhibitor. The alternative approach is adding the test plasma to plasma known to be deficient in a single factor (substrate factor deficient plasma). If there is no correction it means that the patient is defective in that factor. A suggested factor deficiency must be confirmed by specific factor assay. The plasma with factor VIII:C, IX, VII or II deficiency (the last two being prepared in vitro) are relatively widely available, but the plasma with other factor deficiencies such as factor V or X, are not so readily available but can be obtained from commercial sources.

Results from complete hematologic investigations which included correction studies and specific factor assays confirms that this patient had factor V deficiency (Parahemophilia). Specific

factor V assays on father and mother showed moderate decreases of 41 and 47% respectively. According to the reports of other factor V deficient patients,^(11,18,20) the factor V deficient heterozygote possessed factor V levels of 40-52% of normal. From the above results and from the family pedigree (Figure 1), this family is thought to be a case of inherited deficiency of factor V which was transmitted as an autosomal recessive manner though no consanguineous marriage was discovered. Although deficiency of factor V and VIII are often found together, this patient had normal levels of factor VIII. The abnormality in the molecular level will be further studied. Transfusion of fresh frozen plasma seems to be an adequate therapeutical approach for this condition.

Summary

We report here a rare case of isolated factor V deficiency which was probably inherited in an autosomal recessive manner. This disease should be included in the differential diagnosis of patients who show evidence of recurrent minor bleeding with prolongation of routine PT and APTT examinations. Thorough hematologic investigation is necessary before final diagnosis can be made. Except in cases which are combined with other defects the clinical manifestations of factor V deficiency are usually mild and can be easily controlled with transfusions of FFP or FWB.

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