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CASE STUDY

ACQUIRED NEONATAL SEVERE FACTOR II DEFICIENCY- TWO CASES REPORT

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Abstract

In present study two cases of transient acquired and isolated factor II deficiency associated with severe bleeding are reported. Two infants were involved in severe coagulopathy. The blood clot time (CT) in case 2 was excessively prolonged over 16 hours. One-stage prothrombin time (PT) was remarkable prolonged. Haemostatic markers analysis showed an isolated deficiency of factor II at 2.5% and 4.5% respectively. No inhibitory activity against factor II could be detected. We successfully treated the deficiency with vitamin K1 during 15 days. It was interesting that in the case 2 female baby the cause of vitamin K deficiency might be breast feed problem (nutrition deficiency) and/or poor absorption from bowel. Physiopathological laboratory results and therapeutic aspects of two patients were presented.

Keywords: Acquired neonatal factor II deficiency, Plasma factor II activity(II:C) assay, Vitamin K1.

INTRODUCTION

Prothrombin is a precursor to thrombin, an enzyme that convert fibrinogen into fibrin to strengthen a clot (Hemker HC, *et al*; Davie EW and Ratnoff OD; Macfarlane RG; Biggs R; Mial JB). The gene involved in the synthesis of prothrombin is located on chromosome 11, which consists of 14 exons (Girolami A; Lancellotti S). Factor II deficiency (also called hypoprothrombinemia or prothrombin deficiency) was first identified in 1947 by Dr. Armand Quick (Girolami A, *et al*,). Congenital prothrombin deficiency is extremely rare, with an estimated incidence of 1:2,000,000 in the general population (De Bastos O, *et al*, Shusterman S, Manno CS, Key NS, Boles JC, Imane S, *et al*, Lancellotti S, *et al*.,). There were only 100 cases with congenital prothrombin deficiency are known worldwide. Acquired factor II deficiency is caused by several factors: severe liver disease, long-term use of antibiotics, ingestion of vitamin K antagonists such as warfarin, and impaired absorption of vitamin K from the intestines. Newborns may be born with a vitamin K deficiency. The plasma factor II deficiency is associated with a variable bleeding phenotype. Here in this paper, a case 2 with prothrombin deficiency presented the deficiency of vitamin K1 due to poor absorption from the bowel and bile tract.

Case 1:
In May 1985 a 13.5 year old girl had a generalized easy bruising, weakness, and a petechial rash for ten days duration. A joint hemorrhage produces a strict restriction of normal activity. She presented the bleeding gums for three days. There was no family history of bleeding tendency, and chronic hepatitis albeit her hepatochlangiostomy and "T" drain in her right abdomen was performed during early 1982. At the period of the study, she did not use oral warfarin anticoagulants. On examination she developed multiple sites of ecchymosis on the lower part of her legs. Repeat hemorrhages into the left knee, ankle and right elbow caused the limitation of motion activity, and both pain and swelling erosion involving joins surface. A "T" drain was still remained in right lower abdominal cavity without cholangietic jaundice. Blood founding's was hemoglobin (Hb) 83 g/l. The leukocyte count was slightly elevated with $12.5x10^9$/l. The platelet count was $220x10^9$/l. Prothrombin time was excessively prolonged, being over 1260 seconds (control time 12.6 second, (Table 1 and Table 2). She received a week course of vitamin K1 4 mg tid oral administration. The hemorrhagic lesions disappeared. Abnormal coagulant tests recovered to normal (data not shown).

Case 2:

The ten months female baby was admitted to hospital because of pallor, weakness and sporadic subcutaneous ecchymosis from the begin the back purpura to lower part of legs within two days in July 1985. Two days later, hemorrhagic lesions were continuously involved in head, chest, and abdomen even extremities, which were also edematous. Among them, hemorrhagic lesions reached to 5x5 cm after the onset of purpura. No lymphoadenopathy and splenomegaly were found. There was no family history of bleeding tendency. A history of steatorrhea was noticed. She had a normal serum A/G ratio. She did not use oral warfarin anticoagulants.

Table 1: Coagulation studies in two patients with factor II deficiency.

Test	Case 1	Case 2	Case 2 following Vit K1	Control Values
CT (minutes)	72.5	>900,<1260 Clot plug overnight	6	4～12
BT (minutes)	2			1～3
Complete clot Retraction (hours)	3	24		6～24
PRT (seconds)	1290	>1260	134	105～135
Cross-PRT for anticoagulants	No circulating anticoagulants			
PT(seconds) (Quick methods)	>1260	>1260	12.6	11.4～14.7
KPTT(seconds)	930	>1260	31.5	31～38.8
TT (seconds)	15.3	16.4	12.6	13～19
TGT (Biggs method)	No abnormal results			
Factor XIII assay	Normal	Normal		
Factor II activity II:C) (μ/ml)	0.045	0.025		0.596～1.05
VIIIR: Ag(%)		194.5		71.52～173.11

Abbreviation: CT: coagulation time; BT: bleeding time; PRT: plasma recalcification time; PT: prothrombin time (Biggs R, Denson KWE,1967; Mial JB and Lafond DJ,1969a;Quick AJ,1971); KPTT: Kaolin partial thromboplastin time; TT: thrombin time; TGT: thromboplastin generation test; VIIIR: Ag: Factor VIII-related antigen.

On examination, blood founding showed a marked anemia with hemoglobin 22 g/l. The leukocyte count was $4.4x10^9$/l. The platelet count was $376x10^9$/l. Plasma fibrinogen (factor I) 350 mg %. Prothrombin time was excessively prolonged, being over 1260 seconds (control: 11.4～14.7s; Table 1 and Table 2). Thromboplastin generation test (TGT) and plasma factor II activity defined the diagnosis of severe plasma factor II deficiency.

Treatment consists of a small volume (50 ml) of blood transfusion and of 10mg of vitamin K1 administered intravenously, and 2 mg tid of vitamin k1 was given orally. One week later, her hemoglobin recovered to 62g/l, following prompt improved symptoms of anemia. The ecchymotic lesions did not progress, and disappeared. No further hemorrhagic manifestations was observed.

Table 2: Differential PRT, PT and KPTT studies in factor II deficiency.

Test materials	PRT	PT		KPTT	
	Case 1	Case 1	Case 2	Case 1	Case 2
Patient's plasma	1290s	>1260s	>1260s	930s	>1260s
Patient's plasma + normal plasma	150s	13s	19s	44.7s	50.8s
Patient's plasma + normal serum	760s	>1260s	>1260s	262.5s	>1260s
Patient's plasma+$BaSO_4$-absorbed plasma	>900s	>1260s	>1260s	>900s	>1260s
Control values	135s	11s	15s	38.8	41.6s

s: seconds

DISSCUSSION AND CONCLUSION

At present two young infants have been reported with the clinical situation of severe hemorrhagic disease without a history of bleeding tendency in her family. On the basis of *in vitro* experiments it has been suggested that a deficiency of prothrombin might be diagnosed. The laboratory data presented available that prothrombin time was excessively prolonged, which suggest that a defective in mostly involvement of thrombinogenesis (II, V,VII and X deficiency)(phase II of the process of blood coagulation). Failure to correct prothrombin time with the reagents of normal serum (deficient in I, II, V, XIII, but contain "activated" VII, IX, XI and XII) and $BaSO_4$-absorbed plasma (deficient in II, VII, IX and X, but contain I, V, VIII, XI and XII) indicated a deficiency of factor II. The further determination of the factor II activity (II: C) in two patients was 4.3% and 2.5% of normal level respectively. In those cases of factor II deficiency, TGT, as evidence of normal generation of thrombo-plastin and differentiation of plasma factor VIII, IX and XI deficiencies, should be normal time. The normal results of plasma fibrinogen (factor I) and thrombin time, a function of the integrity of the phase III (fibrin formation) of coagulation, reflected no heparin

substances and circulating anticoagulants. It is unknown that the combined deficiency of factor II and mild factor IX in case 2 due to the partial correction of KPTT time with normal plasma. Unfortunately, protein C and protein S, two vitamin K-dependent proteins, were not measured during the period of treatment (Zhu YJ, Li JX; Zhu G, Broekmans AW, Bertina RM).

Prothrombin deficiency is usually characterized by mild to moderately bleeding disorder, and prolonged PT and PTT and normal TT (Shusterman S, Manno CS, Key NS, Boles JC, Roman E, *et al*,. Symptoms include easy bruising, frequent nosebleeds, umbilical cord bleeding and hemorrhage after surgery or trauma. The diagnosis is made based on a low factor II activity and/or antigen measurements. Usually, activity levels less than 10% of normal are found in homozygotes, and between 40 and 60% in heterozygotes (Girolami A, *et al*). In all those vitamin K-dependent factors, including plasma protein C and protein S, are low. Treatment for prothrombin deficiency includes plasma at a dose of 15-25 ml/kg followed by 3 ml/kg every 12-24 hours to achieve levels of approximately 30% (Roman E, *et al*,). PCCs (prothrombin complex concentrates) can be used to the indication of patients with life-threatening bleeds. A minimum targets prothrombin level of 20-30 IU/dl has been suggested for hemostasis (Shusterman S, Manno CS, Key NS, Boles JC). From clinical situation, the pathogenesis of prothrombin deficiency in case 1 was contributed to the vitamin K deficiency. Defective synthesis of vitamin K in case 2,which can result from any long-standing gastrointestinal disorder, particularly in steatorrhea complicated by poor absorption and/or the absence of bile salts in a bowel, may take into account for the explanation of factor II deficiency. Vitamin K deficiency in case 2 may develop during the first few months of life as a result of vitamin K-deficient diet.

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AUTHOR'S CONTRIBUTION

Zhu G: Writing original draft, review, data curation, literature survey, editing, methodology.

DATA AVAILABILITY

Data will be made available on reasonable request.

CONFLICT OF INTEREST

None to declare.

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