Familial Vitamin K Clotting Factor Deficiencies (VKCFD) in an Infant with Novel Mutation in Gamma-glutamyl Carboxylase (GGCX) Gene

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Nongnuch Sirachainan, M.D.[1], Werasak Sasanakul, B.Sc.[1], Rutchanee Kwanchaipanich, M.D.[2], Ampaiwan Chuansumrit, M.D.[1], Praguywan Kadegasem, B.Sc.[1], Pakawan Wongwerawattanakoon, B.sc.[3]

Department of [1]Pediatrics, [3]Nursing, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, [2]Department of Pediatrics, Bhuddasothorn Hospital, Chachoengsao, Thailand

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INTRODUCTION

Vitamin K clotting factor deficiency (VKCFD), a rare bleeding disorder, is an autosomal recessive disorder. Clinical manifestations are ecchymosis, gastrointestinal and renal bleeding, soft tissue hematoma, and bleeding after surgery. The affected enzymes, which have been reported, are ϒ-glutamyl carboxylase (GGCX), and vitamin K epoxide reductase (VKOR). The mutations in either one of the two enzymes, resulting in low level of factors II, VII, IX, and X, have been reported in a few patients.

CASE REPORT

History and physical examinations

- The patient, an eleven-month-old infant girl, was referred to our institute with having had epistaxis and ecchymosis twice since the age of 7 months. The activated partial thromboplastin time (APTT) and prothrombin time (PT) were prolonged. After being given vitamin K 2 mg, intravenously, the patient's coagulogram became normal and bleeding symptom disappeared.
- Physical examination revealed epistaxis and ecchymoses at trunk and extremities, no hepatosplenomegaly and lymphadenopathy.

Feeding history

- She received breast-feeding with 2 meals of solid food containing rice, chicken, fish, and green vegetable. The estimated vitamin K intake from solid food was 45 mcg/day (4.5 mcg/kg/day, maintenance 1-5 mcg/kg).
- Her mother ate all kinds of food including fruits and vegetables. The estimated vitamin K intake was 275 mcg/day (maintenance 90 mcg/day).

Laboratory study

- The APTT and PT were prolonged in patient but normal in parents (Table 1).
- Liver enzyme was normal.
- The levels of prothrombin induced by vitamin K absence II (PIVKA II) were significantly high and slightly high in patient and mother, respectively.
- Genetic study demonstrated heterozygous mutation in ϒ-glutamyl carboxylase gene (Table 1 and Figure 1).

Table 1. Symptoms and laboratory results of patient and parents.

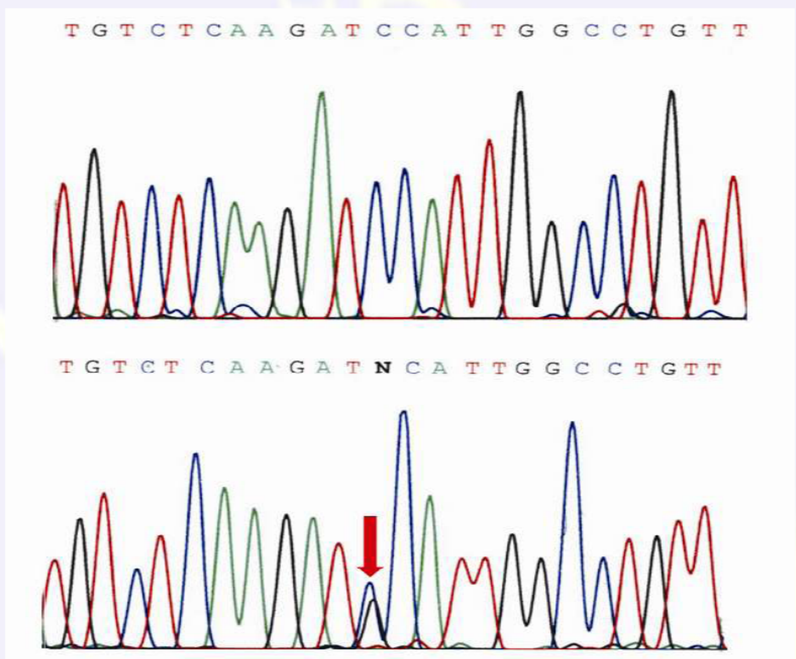
	Patient	Father	Mother
Symptom	Recurrent epistaxis, ecchymosis	None	None
Coagulogram			
• APTT (N 22-28 sec)	231	29	22.8
• PT (N 10-14 sec)	160	10.7	10.8
• INR	15.99	0.9	0.91
• TT (N 9-12 sec)	11.3		
PIVKA II (N<2 ng/ml)	223	1.6	2.79
VKORC1 gene	Normal	Normal	Normal
***GGCX* gene**			
• Nucleotide*	Heterozygous mutation at nucleotide 7973 C>G		Heterozygous mutation at nucleotide 7973 C>G
• Amino acid	Serine to cysteine at position 277		Serine to cysteine at position 277

*Nucleotide positions are specified according to Wu SM, et al. Blood 1997;89:4058-4062.

Treatment and clinical course

- After treatment with vitamin K 2 mg, intravenously, coagulogram became normal.
- Because of the history of recurrent bleeding, regular vitamin K 5 mg, was given intramuscularly every week until the age of 2 years.
- Patient was encouraged to have more food containing high vitamin K, then vitamin K was tapered off to every 2 weeks until stop at the age of 3 years without any symptom. The estimated vitamin K intake was 128 mcg/day (8.5 mcg/kg).
- Six months after stopping vitamin K, coagulogram was normal.

Figure 1. Sequencing of ϒ-glutamyl carboxylase (GGCX) gene show heterozygous missense mutation at nucleotide 7973 C>G.



CONCLUSION

- VKCFD is a rare autosomal recessive inheritance and heterozygous mutation results in recurrent bleeding manifestation during infancy period, although patient has received adequate amount of vitamin K.
- Therefore, regular vitamin K administration is recommended until patient receives adequate amount, more than maintenance level, of vitamin K from diet.