Case Report

Treatment of vitamin K-dependent coagulation factor deficiency and subarachnoid hemorrhage

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BACKGROUND: In adults, vitamin K-dependent coagulation factor deficiency (VKCFD) increases in the recent years. We treated a VKCFD patient with subarachnoid hemorrhage, with favorable outcomes.

METHODS: A 19-year-old male student with VKCFD was treated at our hospital. The initial treatment was injection of a large dose of vitamin K and fresh plasma, and then with oral high dose of vitamin K4.

RESULTS: At 4 weeks after admission, the focus of hemorrhage subsided, neurological examination was normal, and the patient was discharged.

CONCLUSIONS: VKCFD is rare and its diagnosis should be based on the history of the patient and the results of laboratory examinations. A large dose of vitamin K is the first choice of treatment.

KEY WORDS: Vitamin K-dependent coagulation factor deficiency; Subarachnoid hemorrhage; Diagnosis

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INTRODUCTION

With the participation of vitamin K, vitamin K-dependent coagulation factors II, VII, IX and X synthesize in the liver. In the molecular structure of these coagulation factors, there are different numbers of γ carboxyglutamic acid (γ -Gla) residues, which locate in the N-terminal of their own genes.^[1] In physiological conditions, these glutamate residues have γ carboxylation reaction catalyzed by the carboxyl enzyme, while vitamin K is essential for the enzymatic reaction. When vitamin K lacks, the γ carboxylation level decreased in the above coagulation factors, which synthesize in the liver without any function.

Although these abnormal proteins have antigen function, they are not combined with phospholipid and Ca^{2+} in the normal way, and can't play a normal role in blood clotting or anticoagulant activity. This is called vitamin K-dependent coagulation factor deficiency (VKCFD). In adults, VKCFD has been reported to

increase in the recent years. We treated a VKCFD patient with subarachnoid hemorrhage, with favorable outcomes.

Case report

A 19-year-old male student was admitted to a local hospital because of hematuria, low back pain, blood vesicles in the oral cavity, and epistaxis half a month ago. The results of blood examination were normal, and the patient was diagnosed with urinary calculi and nephritis. He was given anti-infective therapy and hemostasis, but the treatment was not sensitive. He was transferred to the 100th Hospital of People's Liberation Army in Suzhou on December 18, 2009. He complained of headache and vomiting for 3 days. Blood routine examination showed WBC $13.5 \times 10^9/\text{L}$, Hb 142g/L, and Plt $333 \times 10^9/\text{L}$. His BP was 130/85 mmHg, and heart rate 86 beats/min. Head CT showed

Figure 1. Brain CT at admission. Head CT showed subarachnoid hemorrhage.

subarachnoid hemorrhage (Figure 1). Ultrasonography of the kidney on both sides showed mild effusion in the left kidney and mild expansion in the upper part of the left ureter. Chest radiograph, electrocardiogram, abdominal ultrasound were normal. The results of urinary red blood cell morphology revealed that red blood cells were of isotype. Glomerular disease was excluded. Routine coagulation tests revealed that activated partial thromboplastin time (APTT) > 120 seconds, prothrombin time (PT) > 120 seconds, thrombin time (TT) and fibrinogen (Fg) were normal. Hemophilia was not excluded. During the course, the patient had no chills, fever, cough, or sputum, but he felt nausea and vomiting. The quality of diet and sleep was poor, but the stool was normal. He was healthy before, and had no history of hepatitis nor long-term of diarrhea or use of antibiotics. He denied the history of gastrointestinal surgery, urinary calculi, bleeding and family history of bleeding.

He was monitored with an ECG monitor, and injected with 1000 ml blood plasma per day for 3 days and 80 mg vitamin K1 daily. After treatment for 6 hours, urine color was bright, and one day after treatment no hematuria appeared. At 3 days after treatment, APTT was 41.6 seconds, and PT 17.4 seconds; TT, Fg, and

vWF were normal. The results of plasma protamine paracoagulation (3P) test were negative. FC: II 81%, FC: VII 34%, FC: IX 37%, and FC: X 63%. At 6 days after stopping the use of plasma, the above clotting factors were tested again and showed a decreasing tendency. After administration of a larger dose of vitamin K1 (a maximum dose of 240 mg/d), the clotting factors returned to normal at 4 weeks. At 2 weeks after admission, head MRI showed that subarachnoid hemorrhage was absorbed, and malformation of cerebral vascular was not observed (Figure 2). The focus of hemorrhage subsided, neurological examination was normal, and the patient was discharged at 4 weeks after admission. After discharge, the patient was injected with 60 mg vitamin K1 twice per week. At 4 weeks after discharge, routine coagulation test showed APTT 74 seconds, PT 55.3 seconds; normal TT, Fg, and vWF; negative 3P test; FC: II 17%, FC: VII 3%, FC: IX 4%, and FC: X 17%. The patient took oral vitamin K4 (240 mg/d), and did not develop any hemorrhage (Table 1). After injection of a large dose of vitamin K1, he experienced side-effects such as flushing, palpitation, which disappeared after slowing down the injection speed. The patient had no side-effects after administration of vitamin K4.

Figure 2. Brain MRI at 2 weeks after treatment. MRI showed that subarachnoid hemorrhage was absorbed, and malformation of cerebral vascular was not observed.

Table 1. The dose of vitamin K and coagulation parameters

Date	ViK4 (mg/d)	FII (%)	FVII (%)	FIX (%)	FX(%)	VWF	APTT (s)	PT (s)	INR	TT (s)	Fig (g/L)	AT-III
2009/12/18	80						145.8	120.0		20.3	4.47	193
2009/12/21	80	81	34	37	63	148	41.6	17.4	1.39	16.3	4.41	127
2009/12/24	80	83	17	60	44		42.1	22.5	1.90	14.0	6.22	127
2009/12/25	120											
2009/12/28	120	94	22	28	44		44.3	20.0	1.64	17.3	5.88	115
2010/1/04	120	72	31	97	45		38.9	18.8	1.53	16.9	4.16	93
2010/1/11	120	78	28	50	52		44.2	19.0	1.55	16.0	4.76	120
2010/1/12	180											
2010/1/18	180	84	35	43	54		38.7	17.2	1.37	15.4	3.72	113
2010/1/20	240											
2010/1/22	240	86	70	96	84		41.0	15.5	1.21	16.4	3.75	111
2010/1/26	240	89	57	90	66		40.3	16.0	1.25	15.6	3.86	126
2010/1/28	60 [#]											
2010/3/01	60 [*]	17	3	4	17		74.0	55.3	5.97	16.4	3.43	96
2010/3/03	100						82.2	57.2	6.23	16.0	3.09	81
2010/3/08	200	9	9	4	19		96.2	43.7	4.43	17.5	3.65	89
2010/3/15	200						47.6	30.0			4.30	
2010/3/20	200						45.6	27.7		14.1	3.70	
2010/3/30	240						47.8	14.8		14.6	3.98	
2010/4/03	240	92	86	76	123		34.6	13.7	1.25	16.3	3.76	93
2010/6/03	200	85	92	89	114		33.8	15.3	1.24	15.2	3.81	87
2010/9/03	160	94	104	87	117		35.6	14.8	1.32	16.4	3.35	97

[#]: intravenous administration of vitamin K1 twice a week; ^{*}: oral vitamin K4 since then.

DISCUSSION

VKCFD is relatively rare, and the severity of hemorrhage differs^[2] because of congenital insufficient intake of vitamin K, intestinal malabsorption, reduced intestinal synthesis, antagonist poisoning, and severe liver disease.^[3,4] At present no diagnostic criteria are

available for this disease. Our patient was diagnosed according to the following criteria: (1) hemorrhage; (2) prolonged or increased APTT, PT, and INR; (3) responsible to high dose of vitamin K1; (4) exclusion of hereditary coagulation factor deficiency disease; (5) decreased activity of coagulation factor II, VII, IX or X.

We consider that the VKCFD patient should be early diagnosed and given a large dose of vitamin K as soon as possible. Weitzel et al^[5-8] reported that administration of a large dose of vitamin K was the first choice of treatment; if a patient had no life-threatening bleeding, plasma or blood products should be reduced. If a patient has bleeding in vital organs such as intracranial bleeding or has unstable hemodynamics, fresh plasma or prothrombin complex plus vitamin K should be administered to increase the levels of blood coagulation factors or correct coagulation disorder. In our patient, 240 mg/d vitamin K was given with good results as reported by Weitzel et al. Since the causes of vitamin K deficiency are unclear, we suggest such patients need a long-term vitamin K treatment and a long-term follow-up.

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