Late-Onset Homozygous Protein C Deficiency Manifesting Cerebral Infarction as the First Symptom at Age 27

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We report a 31-year-old female who had repeated thrombosis and was diagnosed as having congenital homozygous protein C deficiency based on decreased protein C antigen and activity, and the findings of family history. This patient had shown no symptom of thrombosis until the age of 27 years, when she had cerebral infarction as the first symptom. Low molecular weight heparin was useful for disseminated intravascular coagulation (DIC) that complicated protein C deficiency in this patient.

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Key words: DIC, thrombosis, low molecular weight heparin, cerebrovascular disease

Introduction

Congenital protein C deficiency is a genetic disorder that predisposes to thrombosis and embolism (1). We encountered a 31-year-old female who was diagnosed as having congenital homozygous protein C deficiency based on decreased protein C antigen and activity, and the findings obtained by the family history. Disseminated intravascular coagulation (DIC) was also diagnosed according to the diagnostic criteria of DIC proposed by the Research Group of the Ministry of Health and Welfare was treated with low molecular weight heparin (LMW heparin).

Case Report

A 31-year-old female was admitted to our hospital with repeated thromboses. She was well until the age of 27, when she developed disturbance of consciousness while riding a bicycle in 1986. In March 1988, she developed disturbance of consciousness followed by abnormal behavior during housework at the age of 30. Computed tomography (CT) scanning of the head showed cerebral infarction on the left temporal lobe. In the mid-June 1989, she was admitted to another hospital due to increased abdominal pain, watery diarrhea, and vomiting and underwent an operation for necrosis in the sigmoid colon. On July 4, of the same year, left abdominal pain

and mucoid bloody feces appeared, and she underwent an operation at this hospital under the diagnosis of thrombosis in the inferior mesenteric vein. On August 30, pain and swelling in the bilateral limbs developed, and venography of the lower limbs showed deep venous thrombosis peripheral to the thigh. Anti-platelet therapy and treatment with urokinase, heparin, and prostaglandin E₁ (PGE₁) improved the symptoms. Since such thrombosis frequently recurred, she was referred to our hospital on the suspicion of a congenital coagulation abnormality.

In past illness, no abnormalities were detected at her birth and during growth. She had never taken contraceptive pills. In 1986 (at the age of 27 years), she underwent an operation for tubal rupture, but preoperative examination showed no abnormal findings. In familial history, her parents were second cousins (Fig. 1). Her mother died of cerebral thrombosis at the age of 35 years, her paternal grandfather died of cerebrovascular disease (CVA), and her brother died immediately after birth.

On admission, she was 150 cm tall and weighed 67 kg. Her body temperature was 36.6°C. No anemia or jaundice was observed. The chest was normal. In the abdomen, surgical wounds were present, but no tenderness or resistance was noted. The liver, spleen, and kidneys were not palpable. The lower limbs were swollen but showed no flare or tenderness. There were no neuro-

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Protein C			
	Antigen		Activity
	Laurell's method (%)	EIA ($\mu\text{g/ml}$)	Thrombin-activated assay (%)
Patient	0	0.3	5
Family (1)	40	1.8	44
(2)	45	1.7	47
(3)	76	2.8	73
(4)	56	2.0	44
(5)	69	2.6	60
(6)	100	4.4	170

Fig. 1. Pedigree of the patient's family. Family members number 3, 4, 5 and 6 are thought to show partial deficiency (heterozygous protein C deficiency). Closed symbols and a double circle show the deceased members and proband, respectively. The levels of protein C antigen and enzyme activity are indicated in the table. The patient's father, uncles and aunts showed decreased levels of protein C antigen and activity.

logical abnormalities.

Analysis of urine and feces showed no abnormalities (Table 1). The erythrocyte sedimentation rate was 1 mm/h. Though slight anemia was observed, the leukocyte and platelet counts were normal. Blood biochemical and serological examinations showed no abnormal findings. Coagulation tests showed activated partial thromboplastin time (APTT) of 41.3 seconds, prothrombin time (PT) of 16.8 seconds (29%), thrombotest (TT) of 14.0%, and fibrinogen (Fbg) of 83 mg/dl

(Table 2). The plasma level of each coagulation factor was nearly normal. However, the fibrinogen and fibrin degradation product (FDP) level was 29.2 $\mu\text{g/ml}$, and the D-dimer 24.9 $\mu\text{g/ml}$ (normal value 0–0.5 $\mu\text{g/ml}$). FM test also showed a positive result. Regarding the factors inhibiting the coagulation, the antithrombin III (AT III) was 110%, but the protein C antigen level was less than 0.3 $\mu\text{g/ml}$ by the one-step sandwich enzyme immunoassay using a monoclonal antibody which recognizes the Gla-domain of protein C (Teijin, TD-82) (normal value 2.76–3.76 $\mu\text{g/ml}$) (2) and below the detection limit by Laurell's rocket immuno-electrophoresis (3). Protein C activity was less than 5%, which was determined by using protein C-deficient plasma and the protein C-activator (4), but the protein S antigen was 110%. The decrease of platelet aggregation by collagen and arachidonic acid was probably due to the anti platelet drugs administered at the previous hospital. These findings suggested protein C deficiency and DIC.

DIC was improved with treatment with AT III preparation (1,500 U) and LMW-heparin (5,000 U/day). Warfarin (4 mg/day) was used in combination with LMW-heparin to discontinue the latter. However, thrombin/antithrombin III complex (TAT), D-dimer and plasmin- α_2 plasmin inhibitor complex (PIC) gradually increased, and flare, pain, and heat sensation appeared 3 days after the initiation of warfarin administration, and thrombophlebitis developed at upper limbs. Radioisotope fibrinogen uptake study revealed the development of thrombi in the vein of upper limbs. Therefore, the dose of warfarin was reduced to 2 mg/day, and LMW-heparin was continuously used. In addition, fresh frozen plasma (FFP) was administered. Thrombophlebitis improved. At present, ticlopidine is used in combination with these drugs, and no symptoms of thrombosis have been observed.

Familial investigation

The protein C antigen and activity levels in family members who could be investigated are shown in Fig. 1. Her father showed a protein C antigen level of 40% (Laurell's method) (3) and 1.8 $\mu\text{g/ml}$ (EIA) (2), and a protein C activity of 44% (thrombin-activated assay) (4). The paternal and maternal uncles and aunts had no history of thrombosis but showed decreased protein C antigen and activity. The degree of the decrease was less marked in the maternal uncle and aunt.

Discussion

This patient developed transient disturbance of consciousness while pedaling a bicycle at the age of 27 years, left temporal lobe infarction at 30 years, and thromboses in the inferior mesenteric vein and a deep vein in the lower limbs at the age of 31. Examinations to clarify the cause of this frequent thrombosis showed a protein C

Table 1. Laboratory Data on Admission

Urinarysis		Blood chemistry		Na	140 mEq/l
protein	(-)	TP	6.3 g/dl	K	4.0 mEq/l
glucose	(-)	Alb	3.9 g/dl	Cl	108 mEq/l
blood	(-)	T-Bil	0.3 mg/dl	Ca	8.8 mg/dl
ketone	(-)	D-Bil	0.1 mg/dl	P	3.6 mg/dl
Occult blood of stool		GOT	26 IU/l	Serological test	
		GPT	23 IU/l		
		LDH	138 IU/l		
ESR		ALP	136 IU/l	CRP	<0.26 mg/dl
		γ -GTP	290 IU/l	RPR	(-)
		Ch-E	0.98 Δ pH	TPHA	(-)
Peripheral blood		CPK	27 IU/l	ANA	(-)
		FBS	87 mg/dl	RA	(-)
RBC	$341 \times 10^4/\mu\text{l}$	T-Chol	208 mg/dl		
Hb	11.2 g/dl	TG	52 mg/dl		
Ht	34.9%	BUN	12 mg/dl		
Ret	1.1%	Crea	1.1 mg/dl		
WBC	$4,170/\mu\text{l}$	UA	5.1 mg/dl		
Plat	$18.4 \times 10^4/\mu\text{l}$				

Table 2. Hemostatic Test

APTT	41.3 s	ELT	9.5 h
PT	16.8 s	FDP	29.2 $\mu\text{g}/\text{ml}$
TT	14.0%	D-dimer	24.9 $\mu\text{g}/\text{ml}$
Fibrinogen	83 mg/dl	FM	(+)
Factor II	80%	Plasminogen	87.6%
Factor V	93%	α_2 PI	73.4%
Factor VII	70%	Bleeding time	3 min
Factor VIII	68%	Plat retention	39.1%
Factor IX	52%	Plat aggregation	
Factor X	76%	ADP	45%
Factor XI	57%	Adrenaline	11%
Factor XII	57%	PAF	59%
PIVKA II	<1%	Arachid. A	0%
AT III	110%	RIPA	82%
Protein C activity	5%	Cardiolipin antibody	
antigen	0.3 $\mu\text{g}/\text{ml}$	IgG	(-)
Protein S antigen	110%	IgM	(-)

antigen level of less than 0.3 μg (EIA) and below the detection limit (Laurell's method) (Table 2), and a protein C activity of less than 6% (coagulation method). These findings suggested protein C deficiency. This deficiency was considered to be the cause of the frequent thrombosis. In her family history, her mother died of cerebral thrombosis, and paternal grandfather died of CVA. In addition her father showed 40% (Laurell's method) and 1.8 $\mu\text{g}/\text{ml}$ (EIA) protein C antigen, and 44% in the activity of protein C (coagulation method). The paternal and maternal uncles and aunts had no history of thrombosis but showed decreased protein C antigen and activity. These results suggest that protein C deficiency in the proband was inherited from both paternal and maternal sides. i.e., homozygous.

Homozygous protein C deficiency has been reported to develop during the neonatal period and to be a severe

disease repeatedly inducing purpura fulminans (5, 6). However, Manabe and Matsuda reported a patient with homozygous protein C deficiency who showed no symptoms during the neonatal period but developed venous thrombosis at the age of 14 years (7). In the present patient, symptoms suggestive of thrombosis appeared at the age of 27 years, and a definite diagnosis was made at the age of 31 years. The patient reported by Manabe and Matsuda (7) and our patient suggest that homozygous protein C deficiency sometimes produces no symptoms during childhood. Repeated purpura fulminans has also been reported in heterozygous protein C deficiency and is not always specific to homozygous deficiency (8). The development of symptoms of protein C deficiency or abnormality may be affected by the degree of impairment of hemostatic homeostasis in the body caused by quantitative and qualitative protein C abnormalities.

DIC complicating congenital protein C deficiency has been reported in patients with purpura fulminans who developed protein C deficiency during the neonatal period (5, 9-16). Our patient also showed on admission prolonged PT, decreased fibrinogen and increased FDP, fulfilling the criteria of DIC by the Research Group of the Ministry of Health and Welfare. LMW-heparin administration decreased TAT, D-dimer, and PIC. These results suggest the usefulness of LMW-heparin for DIC.

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