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A Family with Hereditary Protein C Deficiency and Brachydactyly Type A3

Takayuki Tominaga [1),2)], *Yoshitaka Nakamori* [1),2)], *Akihiko Taguchi* [1)], *Mutsuko Miyazaki* [1)] *Shizu Sakuragi* [1)] *and Kenji Shinohara* [1)]

[1)] Division of Hematology, Department of Medicine, Yamaguchi Prefecture Central Hospital, Hofu,Yamaguchi 747-8511
[2)] Third Department of Internal Medicine, Yamaguchi University School of Medicine, Ube, Yamaguchi, 755-8505, Japan

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Abstract We diagnosed a patient with deep vein thrombosis with congenital type II protein C deficiency from the mutation in the C-terminal part of the propeptide encoded by exon 3 whose mutation has already been reported. Family study revealed the other affected members of protein C deficiency. The proband and all of the other affected members of protein C deficiency had also shortening of the midphalanx of the little fingers, brachymesophalangia-5, type A3 of brachydactyly. These two abnormalities are co-transmitted by a mechanism which remains to be determined.

Introduction

Protein C is vitamin K dependent and is synthesized by hepatocytes as 461 amino acid polypeptides, and the nucleotide sequences of protein C gene spans 11.2 kb and comprises nine exons. Protein C deficiency is a hereditary disorder causing deep vein thrombosis. Type I deficiency, the most common , is characterized by the reduction of both protein C activity and its antigen due to the reduced synthesis or stability of normal functioning molecules, and in type II deficiency protein C activity is reduced due to the synthesis of abnormal protein C molecules [1)]. More than 160 mutations and 300 patients had been reported by 1995[2)]. We diagnosed congenital heterozygous type II protein C deficiency in a case of deep vein thrombosis who was not diagnosed for many years, identified the nucleotide substitution in exon 3, whose mutation has already been reported[1)], surveyed the family and found the other heterozygous members.

Shortening of the metacarpal and phalangeal bones (brachydactyly) may be found in various congenital hand anomalies, and is classified into five types, A,B,C,D and E[3)-5)]. Short middle phalanges are the main feature of type A brachydactyly, of which ther are several subtypes, A1-A6. In type A3 (BDA[3)], it is confined to the middle phalanx of digit 5, brachymesophalangia-5, is frequently found in Japanese origin, and may be a normal variation[6)]. In our case, brachymesophalangia-5 was observed concomitantly in all of affected family members with protein C deficiency.

The protein C gene is mapped on the chromosome 2q13-q14 (Online Mendelian Inheritance in Man (OMIM) 2000)[7)]. Several brachymesophalangia genes are mapped on chromosome 2q35-36, and 2q37[7)], although the locus for type A3 has not been identified yet. We speculate that these two abnormalities in our case were co-transmitted by the mechanism which remains to be determined.

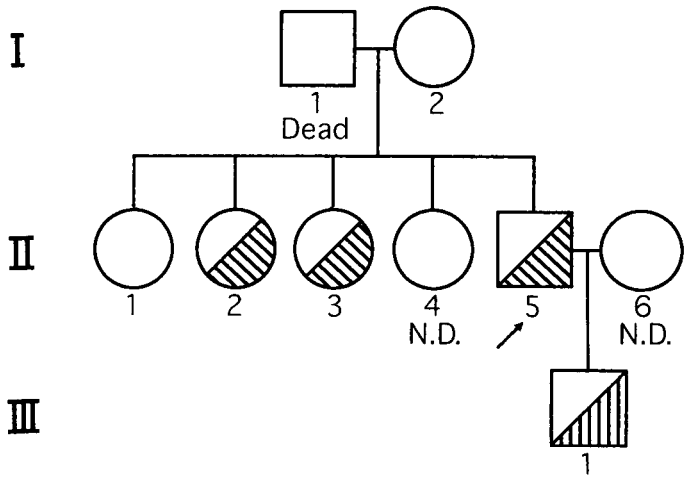
Case Report

The family tree is shown in Fig. 1. A

proband of 52-year-old male (II-5) had suffered from deep vein thrombosis of the lower extremities for twenty years. He was also recently diagnozed with occulusion of the inferior vena cava, portal vein and splenic vein. He was referred to our clinic to investigate the cause of deep vein thrombosis. Hemostatic study revealed ; prothrombin time (PT) 12.5 sec, activated partial thromboplastin time (APTT) 28.4 sec, fibrinogen 345. 7mg/dl, fibrin-fibrinogen degradation product (FDP) 3.1μg/ml, D-dimer 0.8μg/ml. Protein C activity was 41% (normal value ,60-146), and that of the antigen was 106% (70-150). Protein S activity was 86% (73-121).

The patient had no other diseases, nor took special medicine such as anticoagulant. Congenital heterozygous type II protein C deficiency was diagnosed. Chromosome analysis of peripheral blood leukocytes by G-banding was normal. A family study revealed that two other sisters and a son also had a deficiency of protein C activity, hetrozygotes, but these members were asymptomatic for protein C deficiency. Direct sequencing of protein C DNA through exon 1 to exon 9 of the proband revealed a nucleotide mutation of 1387 C→C/T (CGT→TGT) located in the C-terminal part of the propeptide encoded by exon 3, which resulted in an amino acid substitution, Arg→Cys[1]. Analyses of the mutation in the other affected members of protein C deficiency were not performed.

The proband had shortening of the midphalanx of the little fingers (Fig. 2). According to the criteria of brachymesophalangia-5 based on the methods of measurements by several authors[8]; V-MB/V-ML is 0.67(>0.



	I-1	I-2	II-1	II-2	II-3	II-4	II-5	II-6	III-1
Prot C	N.D.	107	125	50	58	N.D.	41	N.D.	40
V-MB/ V-ML	N.D.	N.D.	N.D.	0.65	0.67	0.67	N.D.	N.D.	0.67
V-ML/ V-DL	N.D.	N.D.	N.D.	0.6	0.5	0.5	N.D.	N.D.	0.6
(V-DL)-(V-ML)	N.D.	N.D.	N.D.	10	9	11	N.D.	N.D.	11

Fig. 1. Family tree of hereditary protein C deficiency which was co-transmitted with brachymesophalngia-5. Shaded symbols indicate the members with heterozygous protein C deficiency (II-2,3 and 5, and III-1), and the arrow indicates the proband (II-5). The father (I-1) died of prostate cancer. □: male, △:female. N.D.: not determined. The bottom column indicates protein C activities and measurements of brachymesophalangia-5. MB=breadth of middle phalanx, ML= length of middle phalanx, DL=length of distal phalanx, V=5th finger.

60), V-ML/V-DL is 0.5 (<0.9) and (V-DL)-(V-ML) is 11 mm(>2.0 mm). (MB=breadth of middle phalanx, ML=length of middle phalanx, DL=length of distal phalanx, V=5th finger). These results satisfied the several criteria for brachymesophalangia-5. This type of brachydactyly is classified as A3, BDA3, according to the international classification[3]. All of the affected members with protein C had also brachymesophalangia-5, while those with normal protein C activities had not.

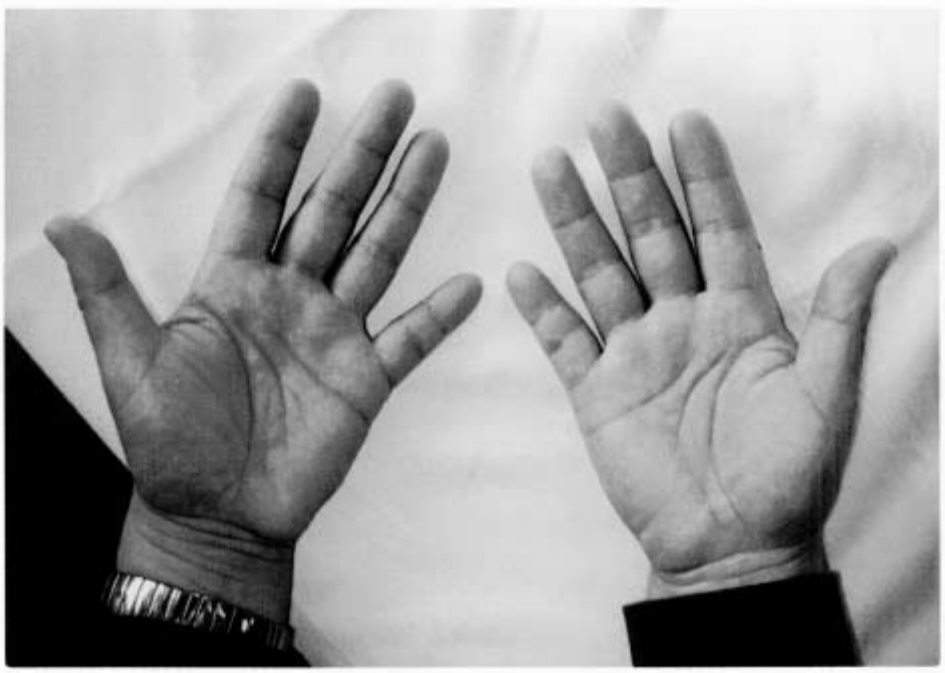


Fig. 2. The proband of protein C deficiency had shortening of the midphalanx of the little fingers, brachymesophalangia-5, and all of the other affected members of protein C deficiency had also this abnormality.

Discussion

The protein C gene is located on the chromosome 2q13-q14[2]. There is a report of a deaf mute with primary hyperoxaluria, dilated cardiomyoptahy, severe hypothyroidism, deep vein thrombosis, arteriovenous graft thromboses, and pulmonary emboli due to protein C deficiency[9]. Some of the patient's family members are also deaf mutes. The authors searched the Online Mendelian Inheritance in Map[7], and found that the long arm of chromosome 2 (2q) includes the loci of type 1 primary hyperoxaluria (2q36-37); type 16 autosomal dominant deafness (2q23-24.3); congenital hypothyroidism due to thyroid dysgenesis or hypoplasia (2q12-14); and dilated cardiomyopathy types 1H, 1G, and 1I (2q14-22,q31, and q35, respectively) as well as that of protein C, and speculated that a defect affecting 2q may have accounted for the complex clinical picture[9].

Several encoding genes for brachydactyly are mapped around 2q35-37; type A1 (BDA 1) on 2q35-36[10], type E(BDE) on 2q37, and bradydactyly-mental retardation syndrome (BDMR) on 2q37[7]. There are recent reports of a novel locus for type A1 on 5p13[11] and for type B on 9q22[12] although the encoding gene for type A3 has not yet been identified.

In the present family, all of the members with protein C deficiency had also brachymeso phalangia-5 inherited by autosomal dominant manner. Such a case had not been reported. However, the results do not suggest casual accordance of transmission, since the encoding genes of protein C and some of brachydactyly are mapped on chromosome 2q, although the mechanism of transmission of these abnormalities remains to be determined.

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