

Accelerated Brain Infarction in Hypertension Complicated by Hereditary Heterozygous Protein C Deficiency

Seiji Kazui, MD; Yoshihiro Kuriyama, MD; Toshiyuki Sakata, PhD;
Masahiko Hiroki, MD; Kotaro Miyashita, MD; Tohru Sawada, MD

Background: Protein C deficiency leads to reduced inhibition of coagulation and an increased likelihood of thrombosis. It is widely accepted that the most common syndromes associated with protein C deficiency are venous thrombosis and pulmonary thromboembolism, whereas arterial thrombosis is rare. Here we describe two patients with hypertension and hereditary heterozygous protein C deficiency who developed multiple lacunar infarcts.

Case Descriptions: Patient 1 was a 46-year-old man with a history of hypertension who developed a right upper quadrantanopia and gradually progressive intellectual and behavioral deterioration. Patient 2 was a 61-year-old man with history of hypertension and two episodes of right-sided motor weakness who developed left sixth and seventh cranial-nerve palsies and reduced pinprick sensation in the right extremities. In both patients, magnetic resonance imaging revealed multiple small lesions in the pons as well as the bilateral basal ganglia, thalamus, corona radiata, and other subcortical structures, which are consistent with lacunar infarcts. Protein C activity and antigen levels were reduced to approximately one half of normal in these two patients, as well as in some of their family members who had no other serological or coagulation abnormalities. A diagnosis of heterozygous protein C deficiency type 1 was thus established.

Conclusions: Although it remains uncertain whether protein C deficiency itself increases the risk of cerebral artery thrombosis, it may predispose a patient to develop multiple brain infarctions in association with hypertension. (*Stroke*. 1993;24:2097-2103.)

KEY WORDS • cerebral infarction • hypertension • protein C

Protein C, a vitamin K–dependent plasma protein synthesized in the liver, is well known to play an important role in regulating coagulation.¹ Activation of protein C is initiated by complex formation between thrombin and thrombomodulin on endothelial cells.² Activated protein C, in conjunction with protein S, is a potent physiological inhibitor of factors Va and VIIIa³ and potentially is an activator of fibrinolysis.⁴ Protein C deficiency thus leads to a loss of clotting system regulation and a propensity for pathological thrombosis.⁵ It is widely accepted that the most common manifestations of this disease are venous thrombosis and pulmonary thromboembolism^{6,7}; however, arterial thrombosis only rarely complicates protein C deficiency.⁸

We recently encountered two patients with multiple brain infarctions associated with hereditary heterozygous protein C deficiency.

Case Reports

Patient 1

A 46-year-old man, a post office clerk with a history of hypertension for 20 years, developed a right-sided visual disturbance 6 months before admission. His colleagues in his office noticed deterioration of his ability to write and calculate. Members of his family also became aware that he was indifferent and depressed. The patient was then admitted to our institute for evaluation of his medical condition on April 25, 1991. He had no arrhythmia, cardiac disease, diabetes mellitus, hyperlipidemia, or smoking habit.

On admission, his blood pressure was 156/96 mm Hg. His pulse was regular at 58 beats per minute. The results of general physical examination were normal. The patient was alert but slightly disoriented to time. On the Mini-Mental State Exam, he scored 23 of 30. Neurological examinations disclosed a right upper homonymous quadrantanopia and exaggerated deep tendon reflexes bilaterally. The hematocrit was 41.7%. Serological tests for syphilis, anticardiolipin antibodies, and lupus anticoagulant were all negative. Magnetic resonance imaging (MRI) studies were carried out using a 1.5-T system (Siemens Corp) with a slice thickness of 4 mm. Axial T1- and T2-weighted images were obtained with spin-echo pulse sequences (T1: repetition time, 600 milliseconds; echo time, 17 milliseconds; T2: repetition

Received February 22, 1993; final revision received August 9, 1993; accepted August 9, 1993.

From the Cerebrovascular Division, Department of Medicine (S.K., Y.K., M.H., K.M., T. Sawada), and the Department of Clinical Laboratory (T. Sakata), National Cardiovascular Center, Suita, Osaka, Japan.

Correspondence to Seiji Kazui, MD, Cerebrovascular Division, Department of Medicine, National Cardiovascular Center, Suita, Osaka, 565 Japan.

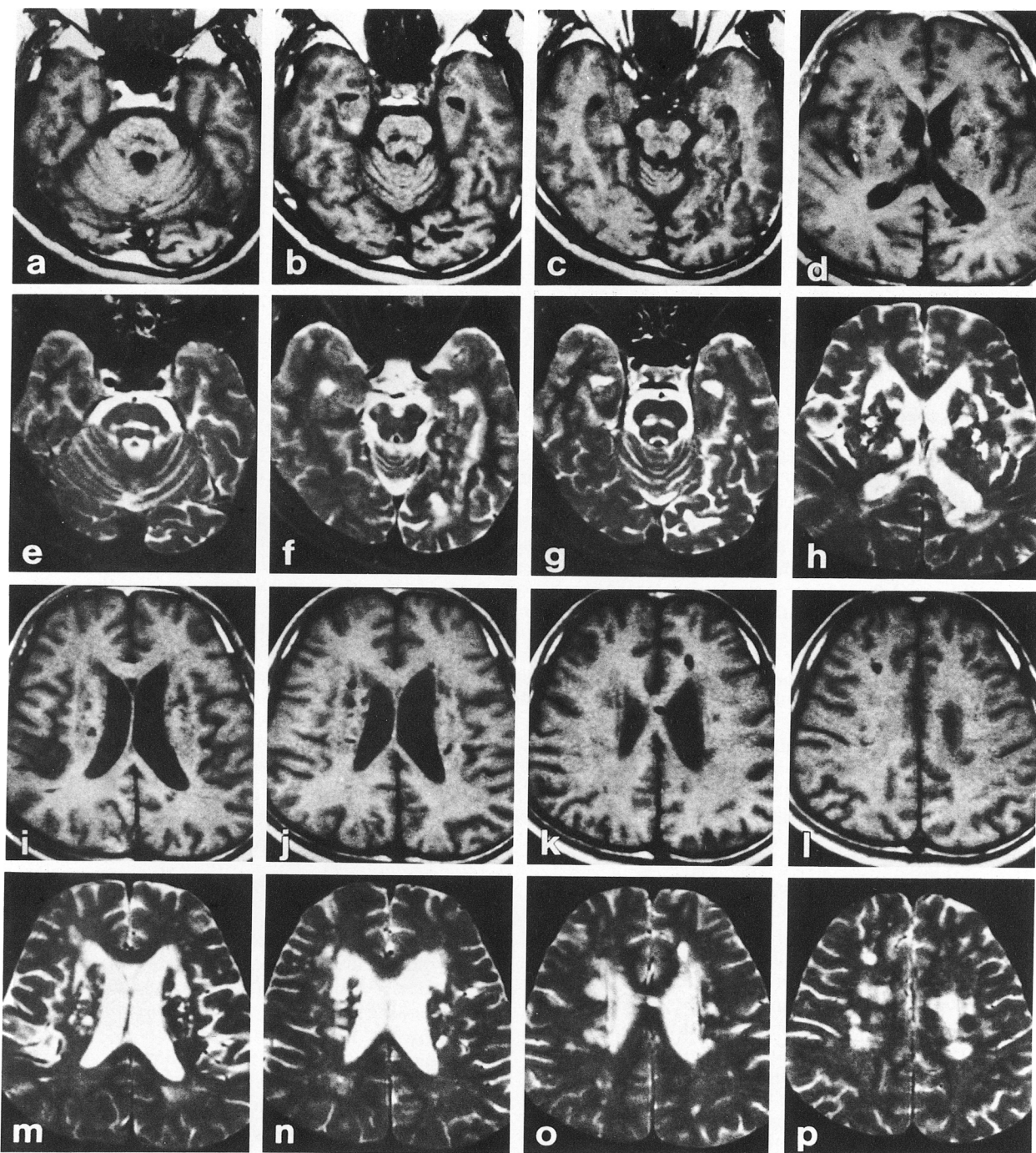


FIG 1. Magnetic resonance images in patient 1 showing numerous areas of low signal intensity on T1-weighted spin-echo images (a-d, i-l: repetition time, 600 milliseconds; echo time, 17 milliseconds) and areas of high signal intensity on T2-weighted spin-echo images (e-h, m-p: repetition time, 2800 milliseconds; echo time, 90 milliseconds) in the pons, left occipital lobe, corpus callosum, basal ganglia, thalami, coronae radiatae, and other subcortical structures.

time, 2800 milliseconds; echo time, 90 milliseconds). T1-weighted images demonstrated numerous areas of low signal intensity in the pons, left occipital lobe, corpus callosum, basal ganglia, thalami, coronae radiatae, and other subcortical structures. These lesions were seen on T2-weighted images as high signal intensity areas. A neuroradiologist (K.M.), who was unaware of the clinical status of the patient, counted 50 lacunar infarcts, in all, on the MRI (Fig 1). Cerebral angiography revealed an occlusion of the left posterior cerebral

artery but no occlusive changes in other extracranial or intracranial arteries (Fig 2).

Patient 2

This patient was a 61-year-old man, an electrical engineer, with a history of hypertension for 13 years as well as two episodes of motor weakness of the right side approximately 10 years before admission. On January 3, 1992, he suddenly developed vertigo with vomiting and inability to walk and was admitted to our institute the

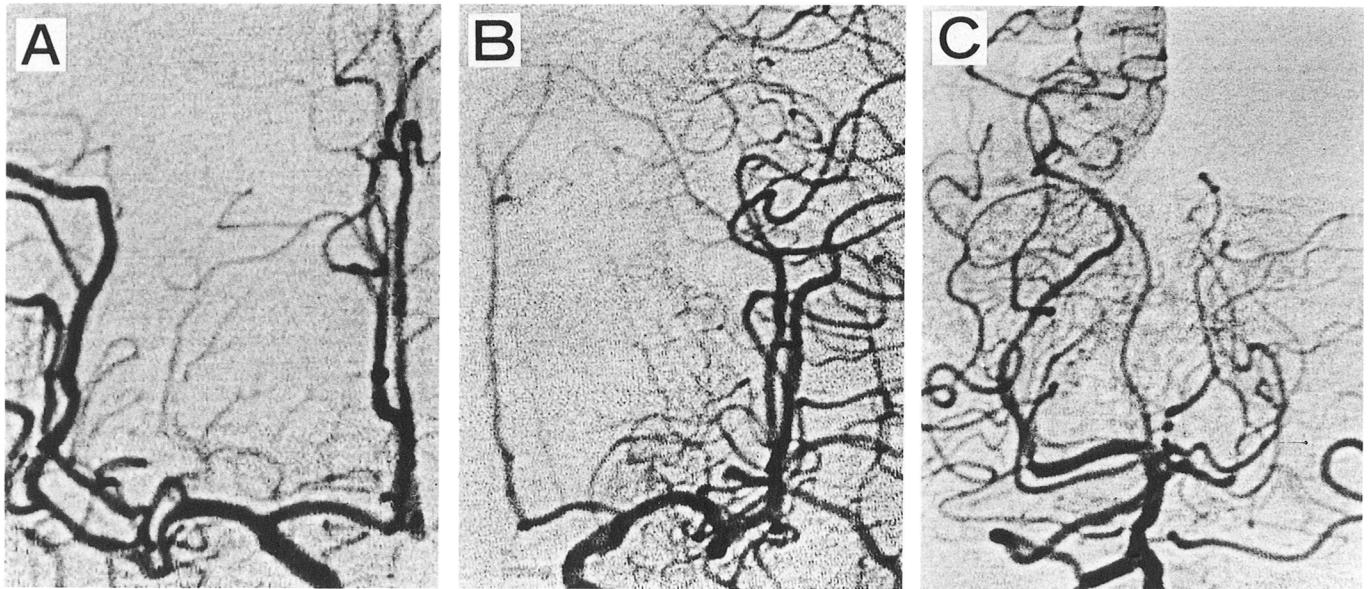


Fig 2. Cerebral angiograms of patient 1. Panels A and B show right and left carotid angiograms, respectively, revealing no occlusive changes. Panel C shows a left vertebral angiogram revealing left posterior cerebral artery occlusion.

next morning. He was a smoker but had no evidence of arrhythmia, cardiac disease, diabetes mellitus, or hyperlipidemia.

On admission, his blood pressure was 176/108 mm Hg. His pulse was 76 beats per minute without arrhythmia. A general physical examination revealed no abnormality. The patient was alert and well oriented to time, space, and person. On the Mini-Mental State Exam, he scored 30 of 30. Neurological examinations disclosed left sixth and seventh cranial-nerve palsies and impaired sensation for pinprick in the right extremities. These findings suggested an infarct on the left side of the pontine tegmentum. The hematocrit was 43.2%. Serological tests for syphilis, anticardiolipin antibodies, and lupus anticoagulant were all negative. MRI studies demonstrated numerous foci of low signal intensity on T1-weighted images, which were found to be hyperintense on T2-weighted images in the pons, internal capsules, basal ganglia, thalami, coronae radiatae, and other subcortical regions (Fig 3). The gadolinium-diethylenetriamine pentaacetic acid infusion study demonstrated marked enhancement in the tegmentum of the left side of the pons. The number of lacunar infarctions totaled 36. Cerebral angiography revealed no occlusive changes in extracranial or intracranial arteries (Fig 4).

Because of the multiple brain infarcts seen in these two patients, coagulation studies were undertaken for the two subjects described and their available family members.

Methods

Coagulation studies were performed approximately 6 months after the onset of stroke for patient 1 and after 1 month for patient 2. The patients were not receiving anticoagulants.

Venous blood samples were collected in 3.8% sodium citrate anticoagulant. Each tube was immediately inverted gently several times and then centrifuged at 3000 rpm for 10 minutes at 4°C. The supernatant was

then placed in plastic tubes and stored frozen at -80°C until used.

Routine coagulation tests, including prothrombin time, activated partial thromboplastin time, and fibrinogen assay were performed according to standard procedures. Fibrin degradation products were measured by the latex coagulation method using LPIA FDP (Teikokuzoki-seiyaku, Tokyo, Japan). Activities of antithrombin III, plasminogen, α_2 -plasmin inhibitor, and factor X were evaluated by the chromogenic substrate method; all kits were obtained from Kabi Vitrum AB (Stockholm, Sweden). C1-inhibitor activity was measured by the chromogenic substrate method (Behringwerke, Marburg, FRG). Plasma prekallikrein was measured with the chromogenic substrate S-2302 from Kabi Vitrum AB. Activities of α_2 -macroglobulin, α_1 -antitrypsin, and plasminogen were assayed by the turbidimetric immunoassay using the corresponding antiserum supplied by Behringwerke. Protein induced by vitamin K absence-II (PIVKA-II) was measured with the PIVKAL test (Teikokuzoki-seiyaku). Protein C antigen was measured by electroimmunoassay with the protein C test (Teijin, Tokyo, Japan). Protein C amidolytic activity was determined by a thrombin-activated assay with chromogenic substrate S-2236 (Kabi Vitrum AB), and protein C anticoagulant activity was measured using commercially available kits from Diagnostica Stago (Asnières-Sur-Seine, France). Free protein S was quantitated by electroimmunoassay using the protein S test (Teijin). Protein S activity was measured according to the method described by Suzuki and Nishioka.⁹ C4b binding protein antigen was measured by a turbidimetric immunoassay using antiserum supplied by Diagnostica Stago.

Results

An isolated decrease of protein C activity was found in both patients and in some of their family members.

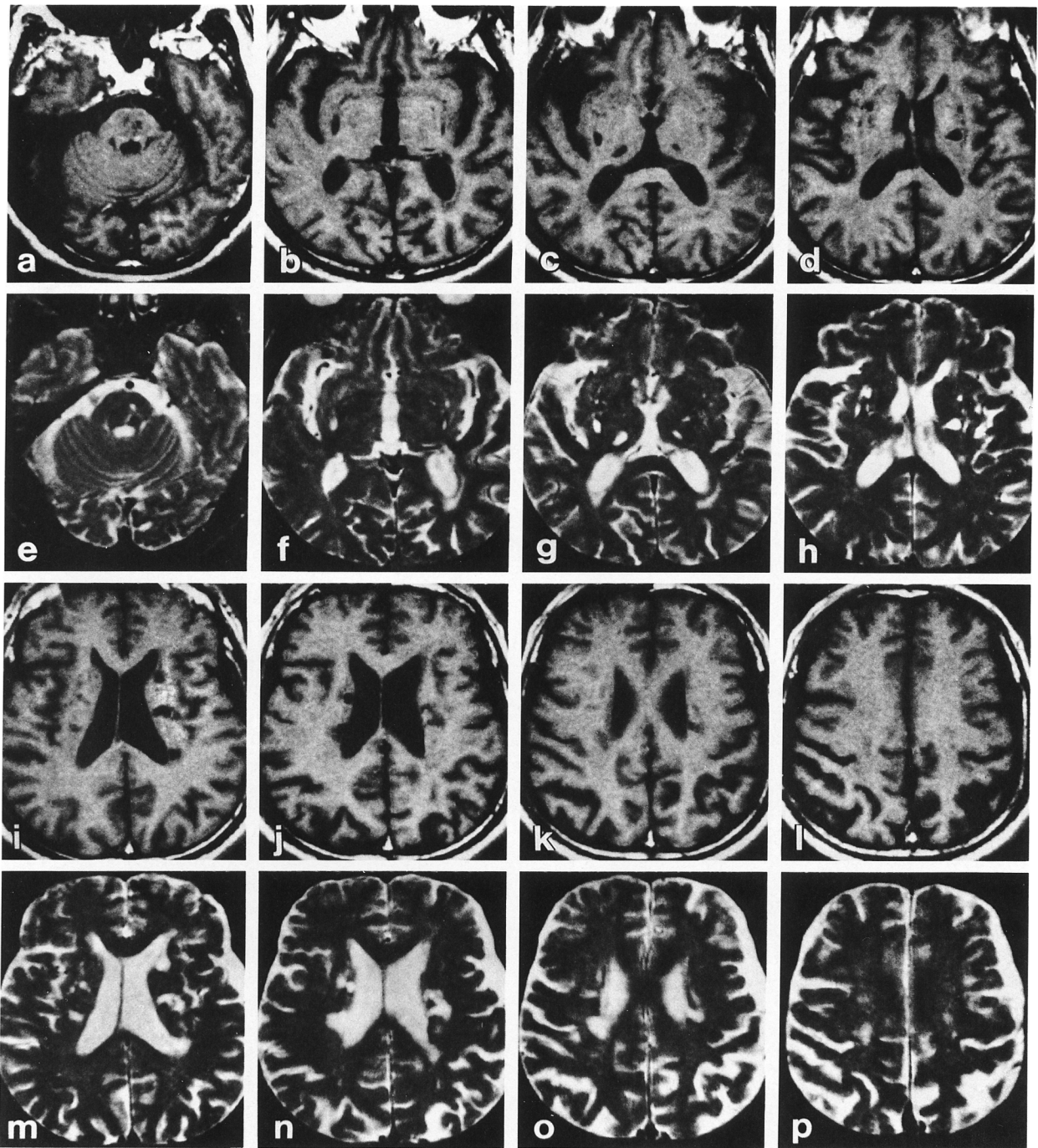


FIG 3. Magnetic resonance images in patient 2 demonstrating numerous foci of low signal intensity on T1-weighted spin-echo images (a-d, i-l: repetition time, 600 milliseconds; echo time, 17 milliseconds), which are hyperintense on T2-weighted spin-echo images (e-h, m-p: repetition time, 2700 milliseconds; echo time, 90 milliseconds), in the pons, internal capsules, basal ganglia, thalami, coronae radiatae, and other subcortical structures.

Patient 1 and His Family

In patient 1, the results of coagulation studies were all within normal range except for protein C levels (Tables 1 and 2). Protein C amidolytic and anticoagulant activities were found to be 52% and 54%, respectively, and the protein C antigen level was also reduced to 54%. Thus, a diagnosis of heterozygous protein C deficiency type 1 was established in this patient. The mother and two sons of the proband, who were asymptomatic, also had protein C concentration of approximately one half

of the normal range; however, his brother and sister had normal protein C levels (Table 2).

Patient 2 and His Family

A diagnosis of heterozygous protein C deficiency type 1 was also established in patient 2, because protein C amidolytic and anticoagulation activities were reduced to 43% and 50%, respectively, and the protein C antigen level was at 57%, while the results of other coagulation studies were all within normal range (Tables 1 and 2).

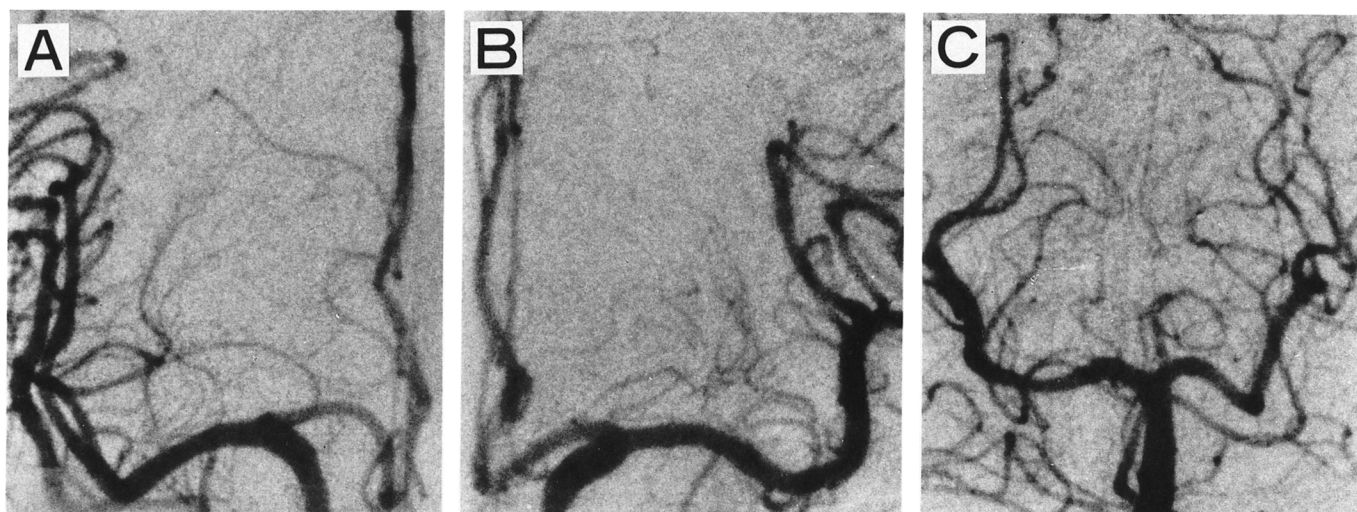


FIG 4. Cerebral angiograms of patient 2. Panels A, B, and C show right carotid, left carotid, and right vertebral angiograms, respectively, revealing no significant stenosis.

The sister of the propositus, who was asymptomatic, also had protein C levels at approximately one half of the normal range; however, his son had a normal protein C concentration (Table 2).

Discussion

There have been several case reports of arterial ischemic stroke associated with protein C deficiency.¹⁰⁻¹⁹ In the majority of these patients, computed tomographic and/or MRI studies revealed large lesions encroaching on the cerebral cortices.^{11,13,14,16-19} Angiography or duplex carotid or transcranial Doppler ultrasonography showed that major cerebral vessels were involved, including the internal carotid,^{12,16,17} middle cerebral,^{11,13,16,19} posterior cerebral,¹¹ and anterior cerebral¹¹ arteries. Some authors^{12,17} have described thrombotic occlusion of the internal carotid artery in association with protein C deficiency, while others^{13,19} have noted recanalization of the middle cerebral artery, which suggested an embolic mechanism.^{20,21}

In the present series, patient 1 had posterior cerebral artery occlusion that caused cortico-subcortical infarction in the occipital lobe, which was classified as atherothrombotic according to the system of the National Institute of Neurological Disorders and Stroke.²² However, the vast majority of the patient's infarcts were small and were located in the basal ganglia, internal capsule, thalamus, corona radiata, centrum semiovale, and pons. These lesions could thus be regarded as lacunar infarcts.²²⁻²⁴

It is well known that lacunar infarcts most often result from the occlusion of small arteries (usually less than 200 μm in diameter) by lipohyalinosis, which is a hypertensive cerebral vasculopathy.²⁵ Our two patients also had a history of hypertension for more than 10 years. Thus, it is unclear whether protein C deficiency itself was the sole cause of infarction in our patients. Their most characteristic MRI findings were multiple lacunar infarcts. It is known that hypertension can cause white matter lesions without stroke symptoms in the

TABLE 1. Coagulation Tests in Patients 1 and 2

	Patient 1	Patient 2	Normal Range
Prothrombin time, %	91	91	79-116
International ratio	1.08	1.06	0.19-1.14
Activated partial thromboplastin time, s	30	35	24-40
Fibrinogen, mg/dL	280	301	150-340
Antithrombin III activity, %	101.7	85.7	80-120
Plasminogen activity, %	100.2	98.6	70-120
α_2 -Plasmin inhibitor activity, %	94.1	93.6	70-110
Fibrin degradation products, $\mu\text{g/mL}$	9	8	<10
C1-inhibitor activity, %	106.9	98	78-120
α_2 -Macroglobulin, mg/dL	167	125	130-350
α_1 -Antitrypsin, mg/dL	209	162	150-260
Plasma prekallikrein, %	81.3	75.5	70-120
Factor X, %	83.2	85.3	70-120
Protein induced by vitamin K absence-II, $\mu\text{g/mL}$	<1	<1	<1

TABLE 2. Protein C Levels and Other Coagulation Parameters in Patients 1 and 2 and Their Family Members

	Sex	Age, y	Antigen	Protein C*		Protein S* (Antigen)	C4 Binding Protein* (Antigen)
				Activity			
				Amidolytic	Clotting		
Patient 1 and relatives							
Patient 1	M	46	54	52	54	91	113
Mother	F	78	49	49	46	88	119
Sister	F	43	83	78	76	99	124
Brother	M	48	85	104	118	94	146
Son 1	M	15	52	66	55	69	76
Son 2	M	18	33	47	41	85	115
Patient 2 and relatives							
Patient 2	M	62	57	43	50	77	107
Sister	F	68	62	50	52	114	190
Son	M	32	100	102	97	98	91
Normal range (n=27)			62-125	66-119	62-122	63-123	70-131

*Values show percentages of normal plasma levels.

elderly.²⁶ However, our patients had small, round, and circumscribed lesions in the basal ganglia and other subcortical regions without any confluent lesions. To avoid overdiagnosis, we defined lacunar infarcts as small subcortical or pontine lesions of decreased intensity on T1-weighted images and hyperintensity on T2-weighted images, according to the recommendation of Shimada et al.²⁷ Fisher²³ performed a detailed pathological study of lacunar infarcts in a series of 1042 consecutive autopsies. In 114 cases, he found 376 lacunar infarcts, with an average of approximately 3 per brain and a maximum of 15 lacunes in a single patient. Ishii et al²⁸ studied 30 necropsy cases of vascular dementia with lacunar infarcts and found that the number of lacunes varied from 6 to 24 per patient. In comparison with these studies, far more lacunes were observed in our patients, since 50 were noted in patient 1 and 36 in patient 2. Miletič et al²⁹ have stated that heterozygous protein C deficiency is not necessarily an important risk factor for thrombosis. In addition, Wong and coauthors³⁰ have reported that the distribution of thrombomodulin varies among the different regions of the human brain, with significantly less thrombomodulin in the putamen, pons, and mesencephalon than in the neocortex. The thrombin-thrombomodulin complex activates protein C approximately 20 000 times more rapidly than thrombin alone.³¹

Therefore, we suggest that protein C deficiency may have accelerated the development of lacunar infarcts in the deep structures of brain in our patients in association with long-standing hypertension. Coagulation studies should be performed in patients with a large number of lacunes, even when they are hypertensive. Our two case reports may help to illuminate the multifactorial pathogenesis of brain infarction. It is to be hoped that a prospective study will be undertaken to investigate the relation between heterozygous protein C deficiency and brain infarction.

References

- Clouse LH, Comp PC. The regulation of hemostasis: the protein C system. *N Engl J Med*. 1986;314:1298-1304.
- Esmon CT. The role of protein C and thrombomodulin in the regulation of blood coagulation. *J Biol Chem*. 1989;264:4743-4747.
- Marlar RA, Kleiss AJ, Griffin JH. Mechanism of action of human activated protein C, a thrombin-dependent anticoagulant enzyme. *Blood*. 1982;59:1067-1072.
- van Hinsbergh VWM, Bertina RM, van Wijngaarden A, van Tilburg NH, Emeis JJ, Haverkate F. Activated protein C decreases plasminogen activator-inhibitor activity in endothelial cell-conditioned medium. *Blood*. 1985;65:444-451.
- Comp PC. Hereditary disorders predisposing to thrombosis. In: Coller BS, ed. *Progress in Hemostasis and Thrombosis*. New York, NY: Grune & Stratton Inc; 1986:71-102.
- Broekmans AW. Hereditary protein C deficiency. *Haemostasis*. 1985;15:233-240.
- Marlar RA, Mastovich S. Hereditary protein C deficiency: a review of the genetics, clinical presentation, diagnosis and treatment. *Blood Coagul Fibrinolysis*. 1990;1:319-330.
- Hart RG, Kanter MC. Hematologic disorders and ischemic stroke: a selective review. *Stroke*. 1990;21:1111-1121.
- Suzuki K, Nishioka J. Plasma protein S activity measured using Protac, a snake venom derived activator of protein C. *Thromb Res*. 1988;49:241-251.
- Israels SJ, Seshia SS. Childhood stroke associated with protein C or S deficiency. *J Pediatr*. 1987;111:562-564.
- Dusser A, Boyer-Neumann C, Wolf M. Temporary protein C deficiency associated with cerebral arterial thrombosis in childhood. *J Pediatr*. 1988;113:849-851.
- Kemkes-Matthes B. Heterozygous protein C deficiency type I. *Blut*. 1989;58:201-206.
- Kohler J, Kasper J, Witt I, Von Reutern G-M. Ischemic stroke due to protein C deficiency. *Stroke*. 1990;21:1077-1080.
- Haire WD, Newland JR. Protein C deficiency and anticardiolipin antibodies in a family with premature stroke. *Am J Hematol*. 1990;33:61-63.
- Grewal RP, Goldberg MA. Stroke in protein C deficiency. *Am J Med*. 1990;89:538-539.
- Camerlingo M, Finazzi G, Casto L, Laffranchi C, Barbui T, Mamoli A. Inherited protein C deficiency and nonhemorrhagic arterial stroke in young adults. *Neurology*. 1991;41:1371-1373.
- De Stefano V, Leone G, Micalizzi P, Teofilii L, Falappa PG, Pollari G, Bizzi B. Arterial thrombosis as clinical manifestation of congenital protein C deficiency. *Ann Hematol*. 1991;62:180-183.
- Gordon BG, Saving KL, McCallister JA, Warkentin PI, McConnell JR, Roberts WM, Coccia PF, Haire WD. Cerebral infarction associated protein C deficiency following allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 1991;8:323-325.
- Matsushita K, Kuriyama Y, Sawada T, Uchida K. Cerebral infarction associated with protein C deficiency. *Stroke*. 1992;23:108-111.

20. Irino T, Taneda M, Minami T. Angiographic manifestations in postrecanalized cerebral infarction. *Neurology*. 1977;27:471-475.
21. Mohr JP, Barnett HJM. Classification of ischemic strokes. In: Barnett HJM, Stein BM, Mohr JP, Yatsu FR, eds. *Stroke*. New York, NY: Churchill Livingstone, Inc, 1986;1:281-291.
22. Special Report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases, III. *Stroke*. 1990;21:637-676.
23. Fisher CM. Lacunes: small, deep cerebral infarcts. *Neurology (Minneapolis)*. 1965;15:774-784.
24. Mohr JP. Lacunes. *Stroke*. 1982;13:3-11.
25. Fisher CM. Lacunar strokes and infarcts: a review. *Neurology (NY)*. 1982;32:871-876.
26. van Swieten JC, Geyskes GG, Derix MMA, Peck BM, Ramos LMP, van Latum JC, van Gijn J. Hypertension in the elderly is associated with white matter lesions and cognitive decline. *Ann Neurol*. 1991;30:825-830.
27. Shimada K, Kawamoto A, Matsubayashi K, Ozawa T. Silent cerebrovascular diseases in the elderly: correlation with ambulatory pressure. *Hypertension*. 1990;16:692-699.
28. Ishii N, Nishihara Y, Imamura T. Why do frontal lobe symptoms predominate in vascular dementia with lacunes? *Neurology*. 1986;36:340-345.
29. Miletich J, Sherman L, Bronze G Jr. Absence of thrombosis with heterozygous protein C deficiency. *N Engl J Med*. 1987;317:991-996.
30. Wong VLY, Hofman FM, Ishii H, Fisher M. Regional distribution of thrombomodulin in human brain. *Brain Res*. 1991;556:1-5.
31. Esmon CT, Owen WG. Identification of an endothelial cell cofactor for the thrombin-catalyzed activation of protein C. *Proc Natl Acad Sci U S A*. 1981;78:2249-2252.