Cerebral haemorrhagic infarction in young patients with hereditary protein C deficiency: evidence for "spontaneous" cerebral venous thrombosis

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Abstract

Among 53 patients with hereditary protein C deficiency belonging to 20 families three women were encountered who, aged 27, 34, and 38 respectively, had had cerebral haemorrhagic infarction, probably due to intracranial venous thrombosis. All three had also had venous thrombosis of the leg and pulmonary embolism either before or after their cerebral infarction. One patient sustained cerebral infarction while receiving an oral contraceptive, but infarction in the two others occurred "spontaneously." One patient also had an intraventricular and subarachnoid haemorrhage during the induction phase of coumarin treatment, which was assumed to have resulted from haemorrhagic infarction of the chorioid plexus, analogous to coumarin provoked haemorrhagic skin necrosis in protein C deficiency.

Hereditary protein C deficiency should be considered in young patients with acute or subacute cerebral symptoms, especially if they have a family or personal history of venous thromboembolism.

Introduction

Hereditary protein C deficiency has recently been shown to carry a high risk of venous thrombosis and embolism.[1-3] Most reports concern heterozygotes with a history of superficial thrombophlebitis, deep venous thrombosis, or pulmonary embolism, or a combination of these, occurring at a young age and without apparent cause. The clinical events in protein C deficiency are most probably related to the important role of protein C in the formation and degradation of fibrin. Protein C is a vitamin K dependent coagulation factor, which, in its activated form, is capable of inactivating the cofactors V and VIII C and of stimulating fibrinolysis.[4-6] In a search to clarify the clinical effects of protein C deficiency we encountered two patients with this disorder suffering from venous thromboembolism as well as cerebral events at a young age, probably as a result of cerebral venous thrombosis. A third patient, who had a history of deep vein thrombosis and pulmonary embolism and who was protein C deficient according to family history, died of cerebral haemorrhagic infarction. We report on these three patients and discuss the implications for diagnosis and treatment.

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Case report

CASE 1

In 1978 a 27 year old woman suddenly had three generalised epileptic fits within one hour after one week of diffuse headaches. She had been using an oral contraceptive. Findings from general and neurological examinations were unremarkable. Computed tomography (fig 1) was compatible with a right frontal haemorrhagic infarction. Right carotid angiography showed thrombosis of the frontal part of the superior sagittal sinus with lack of filling of the corresponding cortical veins (fig 2).

In February 1984 she was admitted to hospital because of a deep venous thrombosis of the right leg. She was successfully treated with streptokinase for two days and subsequently with intravenous heparin and oral phenprocoumon. Five days after starting heparin and

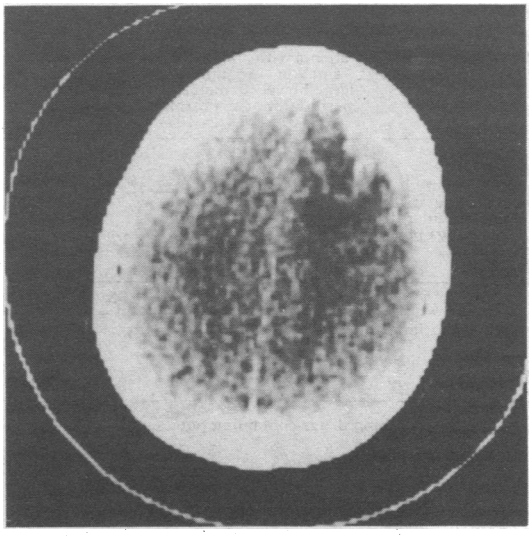

FIG 1—Computed tomogram (case 1) showing right frontal haemorrhagic infarction.

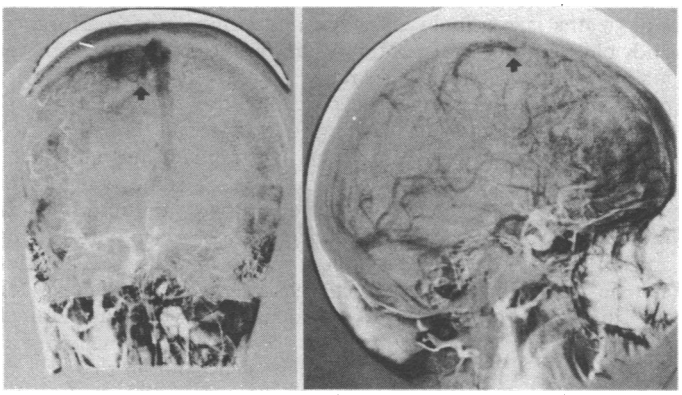

FIG 2—Right carotid angiograms showing thrombosis of frontal part of superior sagittal sinus. An engorged vein is visible at the end of the patent part of the sinus (arrow).

phenprocoumon she complained of headache and neck pain and vomited. A computed tomogram was normal. Two days later she was found in a comatose state. Prothrombin time (with Thrombotest) was excessively prolonged, being 326 seconds (control time 44 seconds). A computed tomogram showed blood in the basal cisterns (fig 3). Maximum density, however, was seen within the fourth ventricle, which apparently contained a blood clot obstructing the cerebrospinal fluid pathway causing appreciable hydrocephalus of the lateral and third ventricles (figs 4 and 5). A ventriculocardiac drain was inserted after neutralisation of the anticoagulant effect, and she regained consciousness within hours.

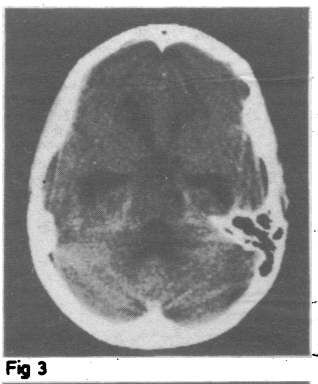

Fig 3

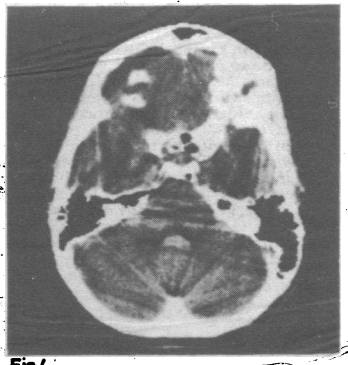

Fig 4

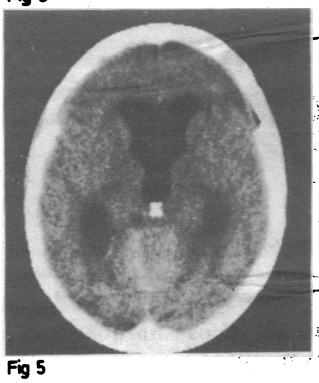

Fig 5

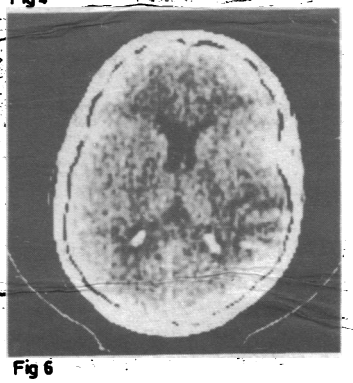

Fig 6

FIG 3—Computed tomogram (case 1) showing haemorrhage in basal cisterns. FIG 4—Computed tomogram (case 1) showing dense haemorrhage in fourth ventricle. FIG 5—Computed tomogram (case 1) showing dilatation of third and lateral ventricles. FIG 6—Computed tomogram (case 2) showing right parietal haemorrhagic infarction.

During the next two weeks she suffered from attacks of breathlessness with tachycardia. Pulmonary perfusion scintigraphy and digital venous imaging confirmed the clinical diagnosis of multiple pulmonary emboli. In the meantime protein C deficiency had been detected (protein C activity 0·48 U/ml; protein C antigen concentration 0·45 U/ml). During this period she did not receive coumarin drugs, the prothrombin time was normal, and there was no evidence of disseminated intravascular coagulation.

Cerebral angiography, four weeks after the subarachnoid haemorrhage, showed a constant contrast accumulation compatible with an apical basilar artery aneurysm. The suspected area of the basilar artery was surgically explored, but instead of an aneurysm a dense bunch of perforating thalamic vessels was found. During the operation one cortical temporal vein showed greenish patches compatible with remnants of a thrombotic process. After the negative exploration oral anticoagulant treatment was reinstituted and she made a good recovery. Revision of the angiograms showed recanalisation of the right frontal cortical veins but, in comparison with the angiograms obtained in 1978, non-filling of the right sylvian and right internal cerebral veins.

Further investigation showed a family history of venous thromboembolism and protein C deficiency in three siblings.

CASE 2

In 1982 a 38 year old woman woke up in the morning with a severe headache. After getting up she noticed that her gait was unstable and found holding objects with her left hand difficult. In 1974 she had been treated for deep venous thrombosis of the right leg. No neurological abnormalities were found. Computed tomography was performed four weeks after the event; it showed a hypodense area with hyperdense components lateral to the trigonum of the right lateral ventricle, compatible with haemorrhagic infarction (fig 6).

She also had protein C deficiency (protein C antigen concentration 0·45 U/ml; protein C activity 0·42 U/ml). Her mother was reported to have had deep venous thrombosis. A sister had had "spontaneous" thrombosis of the right leg when aged 42 and thrombosis of the left leg after a curettage when aged 44. Protein C assays, however, could not be done in our patient's relatives.

CASE 3

In 1969 a 34 year old woman was found beside her bed in the morning. She was unresponsive and restless and she vomited. She had a history of deep venous thrombosis, with pulmonary embolism in 1967, and had been taking oral anticoagulants since that time.

During the previous few months she had been complaining of severe headaches. On examination she was semicomatose with right hemiplegia and restless movements of the left extremities. Prothrombin time with Thrombotest was 50 seconds. The next morning she suffered a sudden cardiorespiratory arrest. At necropsy recent haemorrhagic infarction of the left basal ganglia was found, but a description of the intracranial veins was not included in the report. Protein C assays could not be carried out, but she was an obligatory heterozygote for the trait as both her sister and one of her daughters were protein C deficient. Their protein C antigen concentrations were 0·55 U/ml and 0·54 U/ml, respectively; their protein C activities 0·57 U/ml and 0·65 U/ml.

Discussion

So far we have studied 53 patients with hereditary protein C deficiency belonging to 20 unrelated Dutch families. Of these patients, 42 (80%) have had a history of venous thromboembolism, often recurrent in nature. In three families we encountered a patient with protein C deficiency who had suffered haemorrhagic brain infarction aged 27, 38, and 34 years, respectively. All three were women. In two the cerebral events had been preceded by episodes of venous thrombosis of the leg. One patient (case 1) was taking oral contraceptives, but otherwise no distinct risk factors for the occurrence of the haemorrhagic infarcts were found. None of the patients had symptomatic arterial disease, hypertension, or a source for arterial embolism.

We believe that the cerebral haemorrhagic infarction in these patients was due to venous thrombosis, the occurrence of which was related to the hypercoagulable state present in protein C deficiency. This assumption is proved by angiographic findings in case 1 and supported by circumstantial evidence in the two other patients: the prodromal headaches, the lack of arterial disease, and the history of venous thrombosis point in this direction. We have not yet encountered arterial thrombotic disease in a patient with protein C deficiency aged below 50. Cerebral venous thrombosis has also been described in patients with other forms of hypercoagulability such as familial antithrombin III deficiency,[7 8] cryofibrinogenaemia,[9] and ill defined disturbances of clot lysis.[10 11]

The pathogenesis of the haemorrhage in the fourth ventricle and subarachnoidal space in the first patient needs further discussion. Based on the findings of computed tomography, angiography, and surgical exploration we assume that the bleeding originated in the fourth ventricle with overflow to the subarachnoid space, with obstructive hydrocephalus as a secondary event. We speculate that the haemorrhage was due to venous thrombosis and haemorrhagic infarction of the chorioid plexus during the initial phase of coumarin treatment, analogous to the hypothetical pathogenesis of coumarin induced haemorrhagic skin necrosis in patients with protein C deficiency.[12–14] During this phase of coumarin treatment the

concentrations of factor VII and protein C decrease rapidly because of their short half lives. The further decrease in the already low protein C activity leads to thrombosis in the microvasculature, which appears to be the site of protein C activation.[15] The microthrombosis is followed by infarction and haemorrhage, enhanced by the lowered factor VII concentration. As haemorrhagic infarction of the chorioid plexus with intraventricular haemorrhage is not a rare finding in intracranial venous thrombosis[16 17] this mechanism may have started the intraventricular bleeding, and the subsequent excessive coumarin effect may have contributed to its profuse nature.

We conclude that cerebral venous infarction due to protein C deficiency should be considered if spontaneous cerebral symptoms occur in young patients, especially if they have a family history of venous thromboembolism.

Critical comments by Professor E A Loeliger are gratefully acknowledged.

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(*Accepted 1 November 1984*)

Serum fructosamine concentration as measure of blood glucose control in type I (insulin dependent) diabetes mellitus

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Abstract

Serum fructosamine activity was studied in 42 patients with type I (insulin dependent) diabetes mellitus and 30 non-diabetic volunteers as an index of blood glucose control. There was a significant correlation both between fructosamine and glycosylated haemoglobin values ($r=0.82$) and between fructosamine and the fasting C peptide concentration ($r=-0.81$). Test results in 14 of the diabetics reflected the mean plasma glucose concentration calculated from 25 serial estimations in a single 24 hour period ($r=0.75$; $p<0.01$) but not the mean amplitude of glycaemic excursion ($r=0.23$; $p>0.05$). Fructosamine concentrations measured in these multiple blood specimens did not change significantly throughout the day (mean coefficient of variation 4·1%) despite wide variability of the respective plasma glucose concentrations (mean coefficient of variation 36·2%).

It is concluded that a single random serum sample analysed for fructosamine concentration provides a simple and reliable assessment of glucose homoeostasis in patients with type I diabetes mellitus.

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Introduction

Blood glucose control is difficult to assess in patients with unstable type I (insulin dependent) diabetes mellitus. Glucose concentrations may fluctuate widely during the day, and multiple daily blood glucose estimations are necessary to characterise the glycaemic state accurately.[1 2] Glycosylated haemoglobin (HbA_{1c}), which reflects integrated blood glucose concentrations over weeks to months, provides a useful alternative measure of diabetic control.[2 3] When the test is properly performed HbA_{1c} concentrations do not vary from day to day,[4 5] offering the convenience of random blood sampling.

We recently described the measurement of serum fructosamine as an index of diabetic control.[6] Fructosamine concentrations correlated with HbA_{1c} and other measures of glycaemia[5] and appeared more useful than HbA_{1c} for monitoring short term (three-six weeks) changes after alterations in the treatment of patients with type II diabetes mellitus.[7] The present study was performed to investigate whether fructosamine provides a reliable index of metabolic control in patients with type I diabetes mellitus.

Subjects and methods

The reference intervals for serum fructosamine, fasting plasma glucose, and HbA_{1c} concentrations were determined in 30 healthy non-diabetic volunteers from the hospital laboratory. Insulin dependent diabetics treated with twice daily injections of short and intermediate acting insulin were from the Auckland Hospital diabetic