Clinical Topics

Effectiveness of long term oral anticoagulation treatment in preventing venous thrombosis in hereditary protein S deficiency

JAN J MICHIELS, JEANNE STIBBE, ROGIER BERTINA, ANDRÉ BROEKMANS

Abstract

In eight of 14 patients who were deficient in protein S and who belonged to two unrelated families thrombosis presented as thrombophlebitis in seven and deep vein thrombosis in six, complicated by pulmonary embolism in four and leg ulcers in two. In four patients superficial thrombophlebitis preceded deep vein thrombosis by one to 11 years. Post-thrombotic varicose veins and venous insufficiency had developed in four patients. In three of those and in a fourth patient symptomatic superficial thrombophlebitis, deep vein thrombosis, and pulmonary embolism did not recur while they were taking oral anticoagulant treatment for six to 12 years. The anticoagulation intensity corresponded to international normalised ratio values of over 2.5.

It is concluded that the benefits of anticoagulant treatment for patients with congenital thrombotic disease are great, and thus it is necessary to make an early diagnosis and treat patients at risk of developing thrombosis.

Department of Haematology, University Hospital Dijkzigt, Erasmus University, Rotterdam, the Netherlands

JAN J MICHIELS, MD, senior registrar in haematology
JEANNE STIBBE, MD, senior registrar in haemostasis

Haemostasis and Thrombosis Research Unit, Department of Haematology, University of Leiden, the Netherlands

ROGIER BERTINA, PHD, biochemist
ANDRÉ BROEKMANS, MD, director, thrombosis service

Correspondence to: Dr J J Michiels, Department of Haematology, University Hospital Dijkzigt, Erasmus University, Dr Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.

Introduction

Congenital deficiencies of anticoagulant factor protein C, protein S, or antithrombin III may cause venous thrombosis.¹⁻¹⁰ Long term oral anticoagulation treatment of patients with symptoms with hereditary antithrombin III deficiency and protein C deficiency seems to be effective in preventing the recurrence of thromboembolism. Few reports of the association between venous thrombosis and hereditary protein S deficiency have been published.⁷⁻¹⁰ The benefits and risks of long term anticoagulation treatment of affected patients with vitamin K antagonists still need to be assessed. We report the effectiveness of long term anticoagulation treatment with coumarin in patients with symptoms with protein S deficiency.

Methods

Total protein S antigen was assessed by means of a two step immunoradiometric assay.¹¹ Immunological assays for protein C, factor X, and factor II were carried out as described previously.^{12,13} Antithrombin III activity was measured using a spectrophotometric assay using S2238 (Coatest; KabiVitrum, Sweden).¹⁴ In patients who were receiving vitamin K antagonists prothrombin times were determined with thrombotest (Nyegaard, Oslo, Norway). Values for protein S antigen in healthy people who are not taking oral anticoagulants range from 0.67 to 1.25 units/ml and in patients on stable oral anticoagulant treatment from 0.33 to 0.74 units/ml.¹¹

CASE HISTORIES

Figure 1 shows the pedigree of family L. Family D has been described in part elsewhere.¹⁰ The table gives details of episodes of venous thrombosis, the sequelae, and the laboratory findings for 14 people with hereditary protein S deficiency in the two unrelated families.

FIG 1—Pedigree of family L with hereditary protein S deficiency.

Family L

The proband, III2, suffered from recurrent superficial thrombophlebitis of the legs for nine years from the age of 29. Thrombosis of the left calf vein and femoral vein was successfully treated with an oral coumarin anticoagulant. When coumarin was discontinued superficial thrombophlebitis of the left thigh occurred and thrombosis of the left calf vein recurred (fig 2). Symptoms were relieved within a few days by intravenous heparin treatment after which an oral coumarin drug was taken. Because extensive superficial thrombophlebitis recurred after treatment with coumarin was stopped long term treatment with phenprocoumon (international normalised ratio 4.8-2.8) was started.

Case III1 suffered from severe, recurrent superficial thrombophlebitis of the right leg and abdominal wall. Case III3 had superficial extending thrombophlebitis of the left leg, which rapidly disappeared during treatment with phenprocoumon. Cases III1 and II2 had a history of superficial thrombophlebitis, deep vein thrombosis, and pulmonary embolism and developed severe leg vein insufficiency with recurrent leg ulcers. Case III7 developed superficial thrombophlebitis followed by deep vein thrombosis of the right leg complicated by bilateral pulmonary embolism during a period of immobilisation.

Family D

The proband II4 (fig 2) suffered from deep vein thrombosis of the left leg complicated by pulmonary embolism shown by chest x ray examination and pulmonary perfusion scintigraphy. He was treated with intravenous heparin and then with phenprocoumon for more than 10 years. Thrombotest values were between 5% and 10% (international normalised ratio 4.8-2.8) for most of the time. Post-thrombotic venous insufficiency with varicose veins developed. After a few months of inadequate treatment with an oral anticoagulant (Thrombotest values 15% to 20%; international normalised ratio 2.1-1.8) right calf vein thrombosis was diagnosed by radionuclide phlebography and echography. He was treated with intravenous heparin and then again with coumarin, which was successful.

Case II5 (fig 2) first developed recurrent superficial thrombophlebitis followed by thrombosis of the left calf vein while taking the oral contraceptive pill for four months. The contraceptive pill was withdrawn and she was given oral acenocoumarol for one year. During her first pregnancy, delivery, and postpartum period prophylactic oral anticoagulation treatment was resumed and was continued for three months after delivery. Superficial thrombophlebitis recurred and was followed by deep vein thrombosis in both legs. After a few days of treatment with high dose intravenous heparin the clinical symptoms were largely relieved. Since that time she has been on anticoagulation treatment with Thrombotest values usually between

5% and 10% (international normalised ratio 4.8-2.8), but superficial thrombophlebitis recurred after a few weeks of inadequate anticoagulation (Thrombotest values of 13-19%; international normalised ratio 2.3-1.9).

Case II6 (fig 2) suffered from deep vein thrombosis of the right leg complicated by pulmonary embolism. He was treated with an oral anticoagulant for six months. Because of recurrent superficial thrombophlebitis and post-thrombotic venous insufficiency diagnosed by phlebography coumarin treatment was restarted. Oedema of the right leg persisted, and leg ulcers occasionally recurred. A few months after oral anticoagulant treatment was stopped pulmonary embolism was diagnosed and confirmed by chest x ray film and pulmonary perfusion scintigraphy. He was treated with heparin and has since been on stable long term anticoagulation treatment (international normalised ratio 4.8-2.8) and thromboembolism has not recurred.

Results

Fourteen patients in two unrelated families, 10 men and four women, fulfilled the criteria for isolated protein S deficiency (table). All were heterozygous for the defect. The first symptoms in eight adults who were protein S deficient occurred at between 17 and 33 years of age as superficial thrombophlebitis in six patients and femoral vein thrombosis with pulmonary embolism in two. In four patients recurrent superficial thrombophlebitis preceded deep vein thrombosis by one to 11 years. The episodes of superficial thrombophlebitis occurred without an apparent reason. The contraceptive pill triggered deep vein thrombosis in one patient (II5, family D) and immobilisation triggered it in one (III7, family L). In three patients the first episode of venous thrombosis occurred spontaneously. Four protein S deficient children have shown no symptoms at 5, 5, 10, and 11 years of age, and two protein S deficient adult women (family D II2, II3) are asymptomatic.¹⁰

Figure 2 shows the effectiveness of long term anticoagulation treatment in four patients with protein S deficiency with symptoms. After treatment was stopped superficial thrombophlebitis recurred in three, deep vein thrombosis recurred in two, and pulmonary embolism recurred in one. While they were on long term and stable oral anticoagulant treatment (international normalised ratio 4.8-2.8) for six to 12 years, thrombotic events recurred in two of these four patients only when treatment was inadequate (international normalised ratio 2.3; see case histories of family D II4 and II5).

Discussion

The findings of this study show that spontaneous recurrent superficial thrombophlebitis was the main presenting symptom in

FIG 2—Effects of long term oral anticoagulation treatment in four protein S deficient patients with symptoms.

Venous thrombosis, its sequelae, and the laboratory findings in 14 patients with hereditary protein S deficiency

Age (year and sex)	Superficial thrombosis (age at first occurrence)	Deep vein thrombosis (age at first occurrence)	Pulmonary embolism	Varicose veins	International normalised ratio	Protein S (units/ml)	Protein C (units/ml)	Factor II (units/ml)	Factor X (units/ml)	Antithrombin III (units/ml)
Family D:										
II2 39F	—	—	—	—	—	0.56	1.03	1.09	0.90	0.97
II3 37F	—	—	—	—	—	0.63	1.25	1.03	1.00	1.04
II4* 35M	—	++ (22)	+	+	3.47*	0.19	0.40	0.42	0.36	1.08
II5* 35F	++ (20)	++ (22)	—	+	2.09*	0.23	0.46	0.35	0.44	0.97
II6* 33M	++ (20)	++ (17)	+	+	4.36*	0.21	0.31	0.38	0.32	1.00
III2 5M	—	—	—	—	—	0.59	0.87	0.99	0.97	0.97
III7 4F	—	—	—	—	—	0.63	0.86	1.02	1.00	1.00
Family L:										
III1 72M	++ (28)	++ (29)	+	+	—	0.57	0.88	0.78	0.80	0.93
III1 39M	++ (33)	—	—	—	—	0.65	1.39	1.00	1.13	1.01
III2* 34M	++ (18)	++ (29)	—	—	3.39*	0.17	0.48	0.46	0.37	0.96
III3* 31M	++ (30)	—	—	—	1.95*	0.26	0.58	0.44	0.49	0.97
III7 42M	++ (23)	++ (31)	+	—	—	0.61	1.30	1.29	1.38	1.13
IV1 11M	—	—	—	—	—	0.54	0.76	1.22	0.74	1.07
IV2 10M	—	—	—	—	—	0.52	0.78	0.90	0.91	1.06
Thrombosis (n=8)	7	6	4	4	Normal range	0.67-1.25 0.33-0.74*	0.65-1.45 0.21-0.68*	0.65-1.45 0.32-0.69*	0.65-1.45 0.23-0.63*	0.85-1.25 0.85-1.25

*Taking an oral anticoagulant drug.

+=One episode; ++=recurrent.

our patients with protein S deficiency, and this preceded deep vein thrombosis in two patients by several years. In four patients with symptoms stopping treatment with an oral anticoagulant was followed by a recurrence of superficial thrombophlebitis, deep vein thrombosis, or pulmonary embolism. Subsequent long term treatment with an oral anticoagulant was effective in preventing superficial thrombophlebitis and thrombosis, though these recurred when treatment was inadequate. Since 1972 Thrombotest values of between 5% and 10% (international normalised ratio 4.8-2.8) have been used in the Netherlands to determine the risk of thrombosis.¹⁵ The results of clinical studies show that general long term coumarin treatment to prevent the recurrence of venous thrombosis requires relatively mild anticoagulation and causes few bleeding complications.¹⁶⁻¹⁸ An international normalised ratio of three should be the aim to maintain the ratio at levels higher than two.^{18,19} The range 13-20% (international normalised ratio 2.3-1.8) for the Thrombotest appeared to be insufficient for preventing venous thrombosis in patients with protein S deficiency with symptoms (family D II4 and II5). Thus it may be concluded that in patients with thrombosis caused by hereditary protein S deficiency the target international normalised ratio should be 3.5. It appears that the reduction of the vitamin K dependent procoagulant factors prevented thrombosis despite the induction of a further decrease of the anticoagulant factors protein C or protein S with coumarin in hereditary deficient patients.

Both quantitative and dysfunctional hereditary deficiencies of protein S have been recognised in association with deep vein thrombosis and pulmonary embolism.⁷⁻⁹ As with hereditary protein C deficiency we noted a high incidence of superficial thrombophlebitis as well as venous thromboembolism in patients with hereditary protein S deficiency,^{20,21} but superficial thrombophlebitis is less often seen in hereditary antithrombin III—for example, in 3% of 160 patients who were antithrombin III deficient.²² Serious thrombotic diathesis in hereditary deficiencies of antithrombin III, protein C, and protein S can be adequately counteracted with coumarin and early recognition and appropriate treatment of patients at risk is necessary. It is worth while looking for a hereditary deficiency in patients under the age of 40 who have had or develop venous thrombosis, especially when there is a strong family history of thrombosis. Subsequent family studies will reveal patients with symptoms. Effective prevention of venous thrombosis starts by giving information to affected people about risk factors such as pregnancy, surgery, trauma, immobility, infection, and

obesity. Women who are deficient should not take the oral contraceptive pill. When a patient is exposed to risks conventional prophylaxis with heparin or coumarin drugs should be started. A history of venous thrombosis calls for lifelong treatment with coumarin.

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