



# ALTERED FIBRIN CLOT PROPERTIES IN PATIENTS WITH CEREBRAL SINUS VENOUS THROMBOSIS: ASSOCIATION WITH THE RISK OF RECURRENCE

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## BACKGROUND

Cerebral sinus-venous thrombosis (CSVT) is a rare disorder with an estimated annual incidence of 3-4 cases per 2 million adults. Several risk factors for CSVT have been shown but in 15-20% of patients, no predisposing factors could be identified. Unfavorable fibrin characteristics including faster formation of denser fibrin clots resistant to lysis represent a novel risk factor for both venous thromboembolism and ischemic stroke.

## OBJECTIVES

We hypothesized that denser fibrin networks displaying impaired lysability characterize patients with CVST.

## PATIENTS AND METHODS

We assessed plasma fibrin clot properties in 50 patients (aged 38.9±9.8 years, 36 women) following the first CSVT unrelated to trauma or malignancy after anticoagulation withdrawal and 50 well-matched controls. Recurrences were recorded during follow-up (18 to 46, median 36 months). Permeation coefficient ( $K_s$ ) was assessed using a pressure-driven system.<sup>1-3</sup> The lag phase of the turbidity curve and the maximum absorbance at the plateau phase ( $\Delta$ Abs) were recorded.<sup>1,4</sup> Clot lysis time (CLT) induced by recombinant tPA added to plasma with tissue factor and phospholipids was determined.<sup>4</sup> Moreover, D-dimer levels formed during tPA-induced lysis were measured in the effluent up to the collapse of the plasma gel and maximum rate of increase in D-dimer ( $D-D_{rate}$ ) with maximum D-dimer concentrations ( $D-D_{max}$ ) were estimated.<sup>1,4</sup> The study was approved by the University Ethical Committee.

## RESULTS

Characteristics of the subjects are presented in Table 1. Comparisons of fibrin clot variables in patients with CVST and controls are presented in Table 2. Figure 1 presents differences in  $K_s$  and  $D-D_{max}$  levels between subjects with and without recurrence of CVST. Clot permeability was lower in CSVT patients than in controls ( $K_s$ , 6.43±0.97 vs. 7.3±1.2 x10<sup>-9</sup> cm<sup>2</sup>, P<0.001) and was associated with prolonged clot lysis time (103.0±16.8 vs. 92.4±16.2 min, P<0.001), lower maximum rate of D-dimer release from clots (0.068 [0.064-0.071] vs. 0.072 [0.067-0.078] mg/L/min, P<0.001) and higher maximum D-dimer levels in the lysis assay (4.39±0.56 vs. 4.19±0.46 mg/L, respectively, P=0.03) (Table 2). CSVT patients had a slightly shorter lag phase (P=0.02) and higher maximum absorbance of fibrin gels on turbidimetry (P<0.001) compared to controls. Deficiencies in natural anticoagulants or antiphospholipid syndrome, and factor V Leiden occurred more often in the patients (p<0.05). CVST recurred in six patients (12%) and was associated with 21% higher baseline fibrinogen (P=0.007), 20% lower  $K_s$  (P=0.04) and 17% greater  $D-D_{max}$  (P=0.01) (Figure 1). Multiple logistic regression showed that only elevated  $D-D_{max}$  (>4.83 mg/L) predicted CVST recurrence (odds ratio 5.1; 95% confidence interval, 1.63-16.19) after adjustment for fibrinogen.

## CONCLUSIONS

CSVT is associated with the formation of more compact plasma fibrin clots and resistance to fibrinolysis, which may predispose to the recurrence.

## REFERENCES

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**Table 1.** Characteristics of patients with CVST and healthy volunteers

	CSVT patients (n=50)	Controls (n=50)	P
Age, years	38.9±9.8	38.4±10.2	0.80
Female, n (%)	36 (72)	35 (70)	0.83
Body mass index, kg/m <sup>2</sup>	26.9±4.0	26.8±4.4	0.91
Risk factors of CVST, n (%)			
Oral contraceptive	14 (28)	11 (22)	0.49
Pregnancy	9 (18)	11 (22)	0.62
Cigarette smoking	10 (20)	15 (30)	0.25
Family history of thrombosis	12(24)	11(22)	0.81
Thrombophilia			
Factor V Leiden	11 (22)	3 (6)	0.04
Prothrombin 20210A mutation	4 (8)	2 (4)	0.68
Deficiency of antithrombin, protein C or protein S and anti-phospholipid syndrome	10 (20)	2 (4)	0.03
Laboratory investigations			
Fibrinogen, g/L	2.98 (2.70-3.27)	2.67 (2.33- 3.67)	0.48
C-reactive protein, mg/L	1.55 (0.70-2.90)	1.31 (0.74-1.99)	0.42
D-dimer, ng/mL	237 (197-340)	276.5 (182-360)	0.5
Tissue plasminogen activator, ng/mL	9.7±2.0	11.0±2.9	0.011
Plasminogen activator inhibitor-1, ng/mL	26.1±6.1	25.3±7.6	0.46

**Table 2.** Coagulation factors in patients with CVST and controls

	CSVT patients (n=50)	Controls (n=50)	P*
$K_s$ , 10 <sup>-9</sup> cm <sup>2</sup>	6.43±0.97	7.3±1.2	<0.001
Lag phase, sec	40 (37-42)	41 (38-44)	0.02
$\Delta$ Abs (405 nm)	0.88 (0.81-0.92)	0.80 (0.76-0.86)	<0.001
CLT, min	103.0±16.8	92.4±16.2	<0.001
$D-D_{max}$ , mg/L	4.39±0.56	4.19±0.46	0.03
$D-D_{rate}$ , mg/L/min	0.068 (0.064-0.071)	0.072 (0.067-0.078)	<0.001

$\Delta$ Abs (405 nm) indicates maximum absorbance of fibrin gels at 405 nm; CLT, clot lysis time;  $D-D_{max}$ , maximum D-dimer levels in the lysis assay;  $D-D_{rate}$ , maximum rate of increase in D-dimer levels;  $K_s$ , permeability coefficient. \*adjusted for fibrinogen

**Figure 1.** Scatterplots of baseline clot permeability ( $K_s$ ; panel A) and maximum D-dimer levels in the lysis assay ( $D-D_{max}$ ; panel B) in patients with recurrence of cerebral sinus venous thrombosis (n=6) versus the remainder (n=44). Horizontal lines denote means.

