PAPER

Cerebral venous thrombosis and plasma concentrations of factor VIII and von Willebrand factor: a case control study

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J Neurol Neurosurg Psychiatry 2007;78:699–701. doi: 10.1136/jnnp.2006.103465

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Received 1 August 2006
Revised 14 December 2006
Accepted 17 December 2006
Published Online First
22 December 2006

Background: High plasma concentrations of factor VIII (FVIII) and von Willebrand factor (VWF) have been recently associated with a moderately increased risk of venous thrombosis, but their roles in cerebral sinus and venous thrombosis (CSVT) have not been addressed. To determine whether elevation of FVIII and VWF is more frequent in CSVT, we analysed plasma levels of FVIII and VWF in a case control study.

Methods: The study population consisted of 25 consecutive patients (of whom nine were excluded) admitted for CSVT to the Department of Neurology, Amiens University Hospital, France, from January 1997 to December 2002, for a general screening for thrombophilia. Sixty-four healthy subjects matched for age and sex formed the group control.

Results: Mean FVIII (CSVT: 167.3 (SD 48.8) IU/dl; control group: 117.9 (39.8) IU/dl; $p=0.001$) and VWF levels (CSVT: 165.4 (76.5)%; control group: 108.5 (27.8)%; $p=0.01$) were significantly higher in the CSVT group. Using the 95th percentile of the control group as the cut off value, elevated FVIII (>190 IU/dl) occurred in 25% (4/16) ($p=0.005$) and elevated VWF ($>168\%$) in 37.5% (6/16) of patients with CSVT ($p<0.001$). Using previously reported cut off values (>150 IU/dl or $>150\%$) showed the same results (FVIII: $p=0.005$; VWF: $p=0.009$).

Conclusion: Our study suggests that elevation of plasma factor VIII levels is the most common prothrombotic risk factor for CSVT. Elevation of VWF is also associated with an increased risk of CSVT but its effect seems to be partly mediated through FVIII.

Cerebral sinus and vein thrombosis (CSVT) is a rare localisation of venous thromboembolic disease. It generally occurs in young or middle-aged adults and accounts for approximately 1% of strokes.¹ Many coagulation disorders have been associated with CSVT.^{2–4}

Several prospective studies showed that high concentrations of factor VIII (FVIII) are associated with a moderately increased risk of venous thromboembolism (VTE).^{5–6} The role of increased levels of von Willebrand Factor (VWF) in VTE remains unclear.^{5–7} Recent studies suggest that the effect of VWF is fully explained by FVIII concentrations.⁵ Indeed, the ABO blood group, which regulates plasma concentrations of both FVIII and VWF, may also play a role in susceptibility to thrombosis.^{8–10}

The increased risk of VTE with elevated levels of FVIII or VWF has been observed in previous studies.^{3–7 11} However, they did not specifically include patients with CSVT^{7 9} or they were incomplete.¹²

The aim of our study was to assess plasma levels of FVIII, VWF and other thrombophilic factors in patients with CSVT in a case control study.

MATERIALS AND METHODS

We included all patients admitted to the Neurology Department, Amiens University Hospital, France, from January 1997 to December 2002, with a diagnosis of CSVT, based on clinical and radiological criteria: the diagnosis of CSVT was considered as definite when at least two of three of the following magnetic resonance signs were observed: hyperintensity in venous sinuses on T1 weighted MRI, absence of blood flow on time of flight sequences and intraluminal filling defect on intravenous contrast injection.

Different sociodemographic and medical variables including age, sex, first symptoms, focal signs, treatment delay, risk factors, thrombus location, number and location of parenchymal lesions (haemorrhagic and non-haemorrhagic) and aetiology

were recorded. The outcome was evaluated between April and June 2003. Following information to patients and their general practitioners, they were invited to an outpatient visit to obtain information on the long term course: (i) search for new event (CSVT recurrence, deep vein thrombosis or any other health problem leading to hospitalisation), (ii) current medications, (iii) presence of any residual symptoms (headache, epileptic seizures, neurological deficit and visual disorders) and functional disability and (iv) thrombophilic screening.

Laboratory haemostasis tests were performed during the follow-up examination on STA-R (Diagnostica Stago, Paris, France), and C reactive protein on BCS (Behring, Paris, France). In patients with CSVT, blood samples were obtained to perform the following tests: quick time, thromboplastin time, haematocrit, haemoglobin concentration, platelets count, fibrinogen, ABO blood group, C reactive protein, deficiency of protein C and protein S, activated protein C resistance, lupus anticoagulant and anticardiolipin antibodies, factors VIII, IX and XII, VWF and homocysteinaemia. DNA studies included 677C>T substitution for the methylene tetrahydrofolate reductase (MTHFR) gene, factor V Leiden and factor II G 20210A gene mutation.

We recruited the control group from 151 voluntary blood donors with no personal history of VTE, as assessed by a medical questionnaire. Informed consent for blood analysis was obtained in all subjects. Sixty-four patients matched (four controls per patient) according to age and sex were randomly selected. The following analyses were performed: quick time, thromboplastin time, haematocrit, haemoglobin concentration, platelets count, ABO blood group, deficiency of protein C and protein S, search for activated protein C resistance, and measurement of factors VIII, IX, XII and VWF.

Abbreviations: CSVT, cerebral sinus and venous thrombosis; FVIII, factor VIII; VTE, venous thromboembolism; VWF, von Willebrand factor

Table 1 Initial risk factors and prothrombotic conditions in patients with cerebral sinus and venous thrombosis

Patient No	Age (y)	Sex	Initial risk factors	Thrombophilia screening	Blood group	FVIII (IU)	VWF (%)
1	57	M	–	Homozygous for MTHFR, heterozygous mutation of factor V gene	B+	188*	200†
2	57	M	–	–	A+	174*	190†
3	46	F	OC	–	A+	151*	120
4	19	F	OC	Heterozygous prothrombin gene G20210A mutation	A+	164*	145
5	65	F	SHT	Homozygous mutation of factor V gene	O+	156*	316†
6	46	F	Mastoiditis + OC	–	O–	138	101
7	33	F	OC	Heterozygous prothrombin gene G20210A mutation, homozygous mutation of factor V gene	O+	96	93
8	55	F	SHT	–	A+	195†	235†
9	23	F	OC	Homozygous mutation of factor V gene	O+	150	124
10	73	F	–	Hyperhomocysteinaemia	O–	300†	340†
11	22	F	OC	Heterozygous prothrombin gene G20210A mutation	AB+	126	100
12	69	M	–	–	A+	193†	153*
13	26	F	OC	Homozygous for MTHFR	A+	97	91
14	51	F	Saccoradiculography	–	A+	215†	105
15	40	F	OC	–	A+	185*	186†
16	67	F	Polyglobulia vera	–	O+	149	148

MTHFR, methylene tetrahydrofolate reductase; OC, oral contraceptive; SHT, substitutive hormonal treatment.

*Values higher than published norms; †values higher than local norms.

Statistical analyses

FVIII and VWF levels were compared between patients and controls using the Student's *t* test. In addition, deviant values of FVIII and VWF were determined using local norms (95th percentiles determined in 151 healthy subjects) and previously reported cut off values (>150 IU/dl for FVIII and $>150\%$ for VWF).⁵ The proportion of increased FVIII and VWF values were compared between groups using Fisher's exact test. Pearson correlation was used to explore the relation between risk factors, VWF and FVIII profile. Statistical analyses were performed with SPSS for Windows version 11.0.

RESULTS

Of 25 patients with CSVT, nine were excluded: five were lost of follow-up, three refused interview and one died of a non-vascular cause. The study population consisted of 16 patients (13 women and 3 men) with a median age of 46.8 years (range 20–73). At the acute stage, headache was the more frequent symptom: four patients (25%) presented with isolated headache and eight with intracranial hypertension, defined by associated papilloedema (focal deficit $n=6$; epilepsy $n=4$). Five patients (31%) had only one sinus occluded on magnetic resonance venography. The initial aetiological workup was performed during hospitalisation.

Median follow-up was 34.5 months (range 11–70). One patient (patient No 15) developed a deep venous thrombosis during the follow-up period but no recurrence of CSVT was observed. One pregnancy without complications (patient No 9) was recorded. Six patients (37.5%) had no sequelae, six had modification of their lifestyle habits (modified Rankin Scale = 1) and four (25%) had focal signs (modified Rankin Scale = 2).

Laboratory screening carried out during the outpatient visit revealed at least a prothrombotic condition in 15 patients (93.75%), including elevated FVIII (table 1).

The 64 matched controls did not differ with regard to age (median 43.9 years; range 19–61) or sex (12 men). None of the

patients with CSVT or controls had elevated C reactive protein levels.

The mean FVIII level was significantly higher ($p=0.001$) in the CSVT group (167.3 (SD 48.8) IU/dl; controls 117.9 (39.8) IU/dl). The mean VWF level was significantly higher ($p=0.01$) in the CSVT group (165.4 (76.5)%; controls 108.5 (27.8)%). Using previously reported cut off values, high levels of FVIII (>150 IU/dl) were more frequent ($p=0.005$) in patients (10/16 = 62.5%) than in controls (15/64 = 23.4%). Elevation of VWF ($>150\%$) was also more frequent ($p=0.009$) in patients (7/16 = 43.8%) than in controls (8/64 = 12.5%). Analyses with cut off values calculated using the 95th percentile (FVIII >190 IU/dl; VWF $>168\%$) showed the same results: high levels of FVIII and VWF were more frequent (both $p<0.009$) in CSVT than in controls (FVIII: CSVT = 4/16 (25%), controls = 1/64 (1.6%); VWF: CSVT = 6/16 (37.5%), controls = 1/64 (1.6%)).

A significant positive correlation was obtained between VWF and FVIII both in the CSVT group ($r=0.66$; $p<0.01$) and in controls ($r=0.52$; $p<0.01$).

DISCUSSION

This case control study of coagulation disorders in a small group of patients with CSVT showed that (1) CSVT is associated with high levels of FVIII and VWF, even after controlling for classical confusion factors and (2) it was not dependant on the presence of other prothrombotic factors. Although this laboratory study was performed approximately 3 years post onset, it is unlikely to have influenced our results because FVIII plasma levels remain stable over time.^{6 13 14}

With regard to FVIII, it is not known whether there is a threshold value above which the risk increases. In the majority of reports, the upper limit of normal levels of FVIII has been defined as >150 IU/dl.⁵ However, more recent studies showed that approximately 10% of normal subjects have elevated FVIII levels^{5 6} and this prompts the use of more specific cut off values, such as the 95th percentile.^{15 16} The use of such conservative cut

off values did not change our main findings, and elevation of FVIII was found to be the most common thrombophilic abnormality in CSVT. This relation between FVIII and CSVT has been studied previously only in a single descriptive series.¹² Its presence was found to be independent of other well established risk factors, a finding already reported in VTE.^{6 13 17}

The role of VWF in arterial thrombosis and VTE remains controversial.^{7 18–20} In our study, elevated VWF was more frequent in patients with CSVT but it was always associated with elevated FVIII.

One major limitation of our study was the small number of patients. For the control subjects, no data were available on ethnicity or oral contraception. Several genetic and acquired factors are known or suspected to influence FVIII levels.¹³ Age and sex in particular appear to be two important factors⁸ and should be taken into consideration when developing clinically relevant cut off values.¹⁶

In conclusion, this study suggests that a high plasma level of FVIII may be a frequent risk factor for CSVT. Future studies involving a large number of patients and using carefully designed normative data are warranted.

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Competing interests: None.

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