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A hypofibrinolytic state in overweight patients with cerebral venous thrombosis and isolated intracranial hypertension

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Abstract Evidence suggests that isolated intracranial hypertension (iIH) is often associated with cerebral venous thrombosis (CVT). In eight patients referred to our Institution for iIH who were later shown to harbor CVT we have performed a comprehensive coagulation work-up, including genetic tests for inherited predisposition to thrombophilia, to clarify the etiology of sinus venous thrombosis. All subjects were women. All but one were overweight. There were high plasma concentrations of D dimer, thrombin-antithrombin complexes or prothrombin fragments 1 and 2, further supporting the neuroimaging diagnosis of CVT. Importantly, seven of eight cases had a raised level of plasminogen activator inhibitor 1, a well known inhibitor of fibrinolysis related to obesity. Tissue plasminogen activator levels were elevated accordingly. Factor V gene mutation was present in one subject, and the 20210 prothrombin gene mutation was found in another individual. Three patients had elevated plasmatic levels of homocysteine. In conclusion, the present study provides solid evidence that impaired fibrinolysis probably related to overweight, acting in concert with other prothrombotic abnormalities, is involved in the pathogenesis of CVT presenting as iIH.

Key words Intracranial pressure · Cerebral venous thrombosis · Coagulation · Thrombophilia · Obesity

Introduction

Idiopathic intracranial hypertension, also known as pseudotumor cerebri, is a relatively common syndrome characterized by symptoms and signs of isolated intracranial hypertension (iIH) without clinical, laboratory, or radiological evidence of a space occupying lesion or hydrocephalus [8]. Although many studies have shown the association of idiopathic intracranial hypertension with obesity, pregnancy, and the use of oral contraceptives [6, 13, 25, 28], its etiology is largely unknown. Recent studies have emphasized that as many as 50–80% of patients with a clinical picture of iIH harbor cerebral venous thrombosis (CVT) when carefully investigated through detailed neuroimaging studies such as cerebral venography [15, 16]. In such cases there may be familial or acquired conditions predisposing to thrombosis [5], but many patients do not display coagulation disorders [15, 16]. The latter are usually obese or overweight women [15, 16]. Most interestingly, there is re-

cent evidence that obesity may trigger a hypercoagulable state and the risk of venous thrombosis, mainly by increasing plasma concentration of plasminogen activator inhibitor 1 (PAI-1) with consequent hypofibrinolysis [14, 20, 29]. It is therefore possible that prothrombotic abnormalities related to obesity occur in such patients. To test this hypothesis we studied a large panel of coagulation variables in eight patients with iIH who were later shown to harbor a sinus venous thrombosis.

Methods and materials

Patients

The study group comprised eight patients (all women) with iIH and CVT who were referred during the previous 42 months. In the same inclusion period three additional patients with idiopathic iIH were also seen. Three of these eight patients were sisters. All of them had an initial diagnosis of iIH based on the modified Dandy criteria [6, 8, 13]. Headache associated with visual disturbances was always the first symptom of the disease. The duration of symptoms prior to diagnosis varied from 1 to 20 months (median of 4.5 months). Their ages at the time of the admission ranged from 19 to 39 years (33.4 ± 6.4). On admission all women but one were clinically overweight or obese (body mass index 28.6 ± 2.6) [4]. One woman (patient 7) had been taking oral contraceptives for over 6 months prior to the onset of symptoms. Three patients had menstrual irregularities; none had systemic hypertension or endocrine disorders. Except for symptoms or signs attributable to increased intracranial pressure, neurological and general examinations were otherwise normal. The results of routine laboratory studies were unremarkable. In all patients cranial computed tomography and routine brain magnetic resonance (MR) examination results were always unremarkable. Four of the eight patients displayed neuroradiological findings suggestive of an empty sella turcica.

In all of these patients the diagnosis of CVT was made by intracranial venous MR angiography, which has proven to be a noninvasive and effective technique for detecting various degrees of venous sinus thrombosis [22, 23]. Images were obtained with a 0.5-T whole-body imaging system (GE), using phase-contrast techniques with three-dimensional Fourier transform sequence acquisitions. This has proven to give a better suppression of background tissue, and to be more sensitive to flow in all directions than time-of-flight techniques [23]. The images were postprocessed with a multiple intensity projection algorithm to create a projection venogram. In all eight patients MR angiography depicted irregular or absent flow in the middle part of both the right and left transverse sinuses, reflecting venous stasis or thrombosis [22, 23]. Moreover, in association with the focal flowing abnormalities there were other signs of vein thrombosis such as the characteristic frayed appearance of the thrombosed sinuses and the visualization of dilated and tortuous collateral veins [22, 23].

Blood sampling

After 12 h of overnight fasting, venous blood (18 ml) was collected in Vacutainer tubes containing 0.1 M sodium citrate in a 1:10 ratio and centrifuged at 3000 *g* for 15 min to obtain platelet-poor plasma which was frozen and stored at –80 °C until analyzed. All samples were collected at our Institute and sent to the laboratory on dry-ice. The hemostatic work-up included an automated measurement of activated partial thromboplastin time (APTT automated, Organon Teknika); a prothrombin-complex assay (to measure factors VII, VIII, IX, X, and XI); the coagulant activity of fibrinogen (by the Clauss clotting method, Mascia Brunelli, Milano, Italy); the functional determination of antithrombin III (Coamatic Antithrombin) and the biological activity of PAI-1 (Ortho Diagnostics Milano, Italy). Protein C activity was determined chromogenically, and the von Willebrand factor antigen, protein C antigen and protein S total antigens were measured by Laurell rocket immunoelectrophoresis and a sandwich enzyme-linked immunosorbent assay [27]. PAI-1, tissue plasminogen activator, and lipoprotein (a) related antigens (Imulyse and Tintelyze) were from Biopool Menarini (Florence, Italy). Their measurements were carried out as previously reported in detail [11]. Commercially available kits were also employed for the determination of D dimer, thrombin-antithrombin complexes (Enzygnost TATmicro Behering, Scoppito, Italy), plasma thrombomodulin (Asserachrom Thrombomodulin, Diagnostic Stago), and prothrombin fragments 1 and 2 (dade Prothrombin F1+2 ELISA, Baxter).

The transition from G to A at nucleotide 1691 of the factor V gene (Factor V Leiden), the G to A transition at nucleotide 20210 of the prothrombin gene, and the C677 T substitution of the methylenetetrahydrofolate reductase (MTHFR) gene were detected as previously described [9, 19]. Anti-phospholipid antibodies were assessed with a standardized enzyme-linked immunosorbent assay [12]. The diagnosis of lupus anticoagulant was carried out as recommended [28]. Seventy-five healthy subjects matched for age and sex served as controls for all blood tests.

Results

The overall blood results for the eight patients are summarized in Table 1. The laboratory investigation supported the diagnosis of vein thrombosis, the plasma concentration of D dimer, prothrombin fragments 1 and 2, or thrombin-antithrombin, being alone or simultaneously elevated in these patients. In this group of patients the hematological study also revealed abnormalities of several coagulation variables. The most consistent finding was an elevated level of PAI-1 (in seven of the eight individuals analyzed). Data on tissue plasminogen activator strengthen the latter finding (see Table 1). Factor V gene mutation was found in one patient, and the G20210 A prothrombin gene mutation was found in another individual. Three patients had elevated plasmatic levels of homocysteine. No subject was homozygous for the MTHFR mutation. Moreover, prothrombin time, activated partial thromboplastin time, thromboplastin time (ratios), total and free protein S (%), plasminogen (%), antiplasmin (%), and factors VIII, IX, X, and XII (%) were all within normal control values. No positivity for a circulating lupuslike anticoagulant was present, as judged by the ratios of the Caolin clotting time and the dilute Russel viper venom test. No patient had a protein C or an antithrombin III deficiency.

Discussion

The present study indicates an abnormally high prevalence of hypercoagulability in patients with a clinical picture of iIH and CVT. Consistent with our observation, other authors [2, 26] have demonstrated a high occurrence of prothrombotic abnormalities in patients with iIH, but

Table 1 Coagulation studies in eight women with isolated intracranial hypertension secondary to sinus vein thrombosis (*F 1+2* Prothrombin fragments 1 and 2, *T-AT* thrombin-antithrombin, *t-PA* tissue plasminogen activator, *FDP* fibrinogen degradation products, *ACA* anticardiolipin antibodies)

	Patients (age, years)								Controls (n = 75; value ± 3 SD)
	1[a] (37)	2[a] (38)	3[a] (35)	4 (37)	5 (36)	6 (29)	7 (19)	8 (36)	
Body mass index	31.5[b]	28.9[b]	22.2	30.4[b]	27.8[b]	29.8[b]	29.6[b]	28.4[b]	< 25
Laboratory tests									
D dimer (ng/ml)	650[b]	145	175	845[b]	345[b]	350[b]	207	312[b]	145 ± 115
F 1+2 (nM)	1.75[b]	1.55[b]	1.05[b]	1.05[b]	0.85[b]	0.75	1.00[b]	1.34[b]	0.48 ± 0.35
T-AT (μg/l)	3.05	2.35	2.65	2.05	3.05	4.05[b]	3.5	3.05	2.2 ± 1.46
Fibrinogen (mg/dl)	298	233	255	205	245	395[b]	307	399[b]	265.5 ± 40.4
PAI-1 (AU/ml)	17.5[b]	21.5[b]	17.5[b]	18.5[b]	9.5	16.5[b]	10.9[b]	18.3[b]	6.2 ± 3.8
t-PA (IU/ml)	11.5[b]	13.5[b]	11.5[b]	10.5[b]	9.5[b]	13.5[b]	5.1	10.7[b]	3.3 ± 1.8
FDP(s) (μg/ml)	10.0[b]	4.0	2.0	12.0[b]	2.0	3.0	3.0	8.0	4.5 ± 3.5
ACA-IgG (GPL U/ml)	9.5	10.5	8.5	5.5	4.5	11.5[b]	8.0	12.0[b]	< 11.0
ACA-IgM (%PL U/ml)	5.5	5.5	2.5	6.5	1.5	6.5	3.5	6.0	< 10.0
Homocysteine (pmol/l)	8.2	11.5	14.4	19.0[b]	17.6[b]	10.8	18.0[b]	16.0	M:11–14, F: < 16
Cyanocobalamine (nm/l)	423	443	317	433	321	704	495	407	200–500
Folate (nmol/l)	4.0	4.2	4.9	4.4	4.8	21	5.5	7.3	4–9
Factor V G1691A gene mutation	–/–	–/–	–/–	–/–	–/–	–/–	–/–	–/+	–/–
G20210 A prothrombin gene mutation	–/–	–/–	–/–	+/–	–/–	–/–	–/–	–/–	–/–
C677 T MTHFR gene mutation	–/–	+/–	–/–	+/–	–/–	–/–	+/–	–/–	–/–; –/+

[a] One of three sisters
[b] Abnormal value

they did not investigated for CVT in these patients. In our series most patients showed elevated circulating levels of the PAI-1 and tissue plasminogen activator antigen. It is now clear that the levels of the latter rise with the increase in PAI-1 inhibition, so that high levels of either factor reflect reduced fibrinolysis [14, 20]. Impaired fibrinolysis is often present in subjects prone to thrombotic events [18, 29]. An elevated body mass index is a major determinant of high PAI-1 plasma levels [14]. Almost all our patients were overweight, thus indicating that an elevated body mass index by impairing fibrinolysis may be a risk factor for CVT. Importantly, many of them also displayed well known genetic or acquired factors predisposing to vein thrombosis such as mutations of the factor V gene and the prothrombin gene, or elevated plasmatic levels of homocysteine [1, 7, 10, 21]. This points to an interaction between an impaired fibrinolysis related to overweight and other prothrombotic abnormalities in the development of CVT presenting as iIH.

Consistent with our observations, there is accumulating evidence that CVT is associated with an inherited or acquired tendency to thrombophilia [7, 10, 21]. In an important study, Martinelli and coworkers [21] recently clarified the roles of genetic and environmental factors in the development of CVT. They demonstrated that the use of oral contraceptives in subjects with the prothrombin gene mutation greatly raises the risk of developing CVT. Clarifying all these risk factors and the extent of their interaction has important implications for individualized treatment and prevention of CVT [3]. In this way, since the lowering of body weight is known to be associated with lowering of PAI-1 plasma levels [14], the results of our study rise the possibility that such patients may benefit from dietary strategies in addition to anticoagulants or thrombolytic treatments.

Finally, particularly noteworthy was the observation that sinus venous obstructions, as detected by MR angiography venography, always involved both transverse sinuses. In accordance with this finding, some studies have shown that these are the preferential site for CVT, especially in patients presenting with less severe symptoms such as iIH [17, 22]. In our patients the presence of venous thrombosis was further supported by the parallel high levels of D dimers, a valuable and specific indicator of deep-vein thrombosis [24].

In conclusion, our study provides strong evidence that an impaired fibrinolysis related to overweight, acting in concert with other prothrombotic abnormalities, is involved in the pathogenesis of CVT presenting as iIH. Further studies are needed to establish whether, in addition to anticoagulants or thrombolytic treatments, the lowering of body weight may be an effective therapeutic strategy in such patients.

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