PRO-COAGULANT IMBALANCE IN PATIENTS WITH CUSHING DISEASE DETECTED BY THROMBIN GENERATION ASSAY IS ASSOCIATED WITH INCREASED LEVELS OF NEUTROPHIL EXTRACELLULAR TRAP-RELATED FACTORS

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OBJECTIVES

Patients with Cushing disease are at increased risk of venous thromboembolism (VTE). It was surmised, but not conclusively shown that the risk is related to plasma hypercoagulability secondary to the effect of glucocorticoids. This study aimed at investigating the thrombin-forming potential of patients with Cushing disease in the presence of a functioning protein C system by adding its main physiological activator, thrombomodulin.

PATIENTS

Forty-eight consecutive patients were enrolled in the study at the time of diagnosis. They were classified as having Cushing Disease according the Endocrine Society Guideline and Consensus Statement . Patients that at the time of blood drawing or during the previous two weeks had taken antithrombotic drugs (heparins, vitamin K antagonists or direct oral anticoagulants) were excluded from the study. Similarly, also women taking estro-progesterone pill were excluded. Forty -eight healthy subjects matched for age and gender with the patient population were chosen as controls.

RESULTS

Under these experimental conditions, which mimic closely the in vivo situation, we observed significantly enhanced thrombin-generation in patients with Cushing disease, as shown by the modification of thrombin generation parameters [i.e.,shortened lag-time and time-to-peak, increased thrombin-peak and endogenous-thrombin-potential (ETP)]. Moreover, the ETP ratio (with/without thrombomodulin), recognized as an index of hypercoagulability, was increased in patients as compared to controls, indicating that patients with CD are resistant to the anticoagulant action of thrombomodulin. We attempted to explain such hypercoagulability by measuring both pro- and anticoagulants factors and some other non-coagulation parameters (i.e., neutrophil extracellular traps (NET), recently associated with the risk of VTE and/or increased procoagulant imbalance.

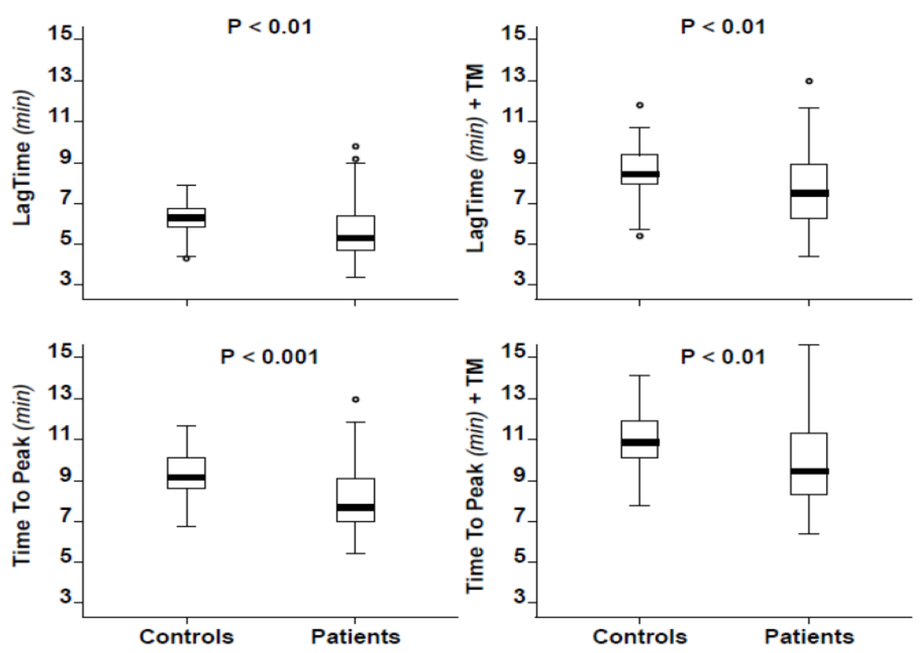

Fig. 1

	Patients (n=48)	Controls (n=48)
Women, n (%)	36 (75.0)	29 (60.4)
Age at diagnosis (yrs)	45 ± 12 (25-76)	42 ± 11 (26-69)
BMI (Kg/m2)	28.1± 6.3	26.3± 4.6
Serum cortisol (mcg/dL)	24.8 ± 9.7	ND
24 hours free urinary cortisol (SDS)	8±6.6	ND
ACTH (pg/mL)	65+54.65	ND
1 mg-DST (mcg/dl)	15.8±10.0	ND
History of DVT (%)	4%	ND

Table 1.

	Patients (48)	Controls (48)
PT ratio	1.01 (0.87-1.35)	1.01 (0.87-1.16)
APTT ratio	0.94 (0.75-1.69)	1.00 (0.81-1.24)*
Factor VIII (%)	139 (80-275)	117 (71-198)**
Von Willebrand factor antigen (%)	166 (66-424)	116 (54-208)***
Von Willebrand factor cofactor activity (%)	164 (51-369)	101 (45-183)***
Factor II (%)	110 (62-145)	98 (72-140)*
Fibrinogen (mg/dL)	300 (175-498)	297 (191-406)
Protein C (%)	138 (87-200)	107 (77-145)***
Antithrombin (%)	123 (72-156)	110 (86-129)***

Table 2

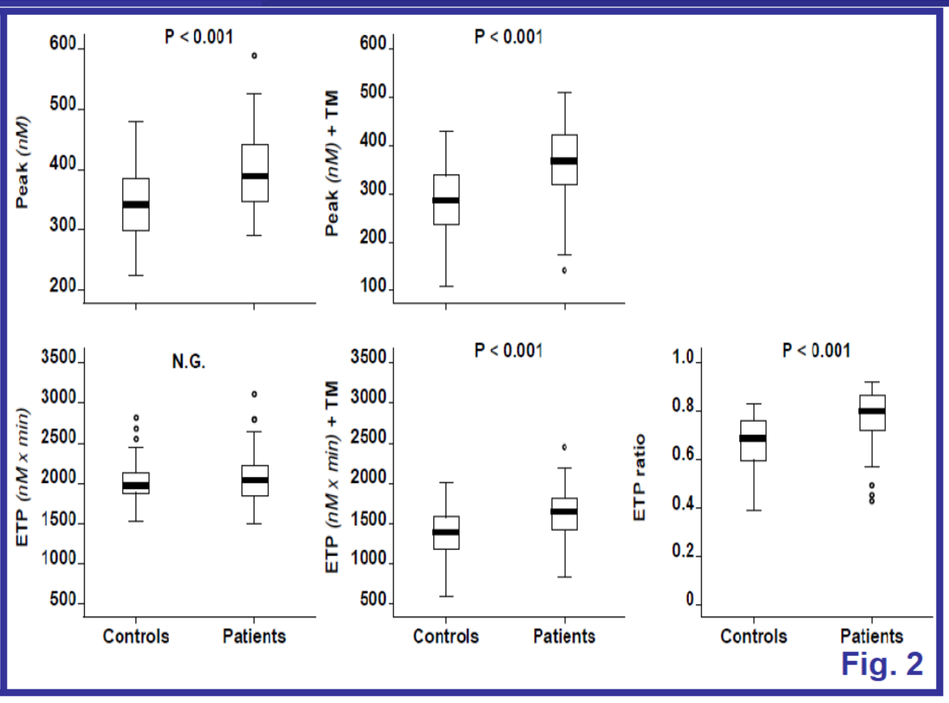

Fig. 2

LEGEND TO TABLE AND FIGURES

Table 1. Main characteristics of patients with Cushing disease and controls.

Table 2. Median (range) levels of studied coagulation variables. *p<0.05; **p<0.01; ***p<0.001

Fig 1. Values for the lag-time and time-to-peak with or without the addition of TM.

Fig 2 Values for the thrombin peak, the endogenous thrombin potential (ETP) with or without the addition TM and for the ETP ratio (with/without thrombomodulin).

CONCLUSIONS

We show that the hypercoagulability detected by thrombin-generation in patients with Cushing disease is associated with increased levels of factor VIII and NET-related variables. Whether this plasma hypercoagulability can entirely explain the occurrence of VTE (first event or recurrence) in patients with Cushing disease should be investigated by ad hoc clinical trials. However, until these studies will be available the evidence for the hypercoagulability supports the concept that patients with CD are candidates for antithrombotic prophylaxis.

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Adrenal cortex (to include Cushings)

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