Coagulation Profile Dynamics in Pediatric Patients with Cushing Syndrome: A Prospective, Observational Comparative Study

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Objective To evaluate the association between Cushing syndrome and hypercoagulability in children.

Study design A prospective, observational study was performed of 54 patients with Cushing syndrome, 15.1 ± 3.9 years, treated at the National Institutes of Health Clinical Center. Coagulation profiles were taken before and 6-12 months after surgery and compared with18 normocortisolemic children, 13.7 ± 3.6 years.

Results At baseline, patients with Cushing syndrome had greater levels of the procoagulant factor VIII (FVIII) vs controls (145 IU/dL ± 84 vs 99 ± 47, $P = .04$); 6-12 months after surgery, FVIII levels decreased to 111 ± 47, $P = .05$. Patients with Cushing syndrome had greater levels of the antifibrinolytic α2-antiplasmin, 96 ± 17% vs 82 ± 26%, $P = .015$. After surgery, antifibrinolytic α2-antiplasmin levels decreased to 82 ± 24%, $P < .001$. Anticoagulants were greater in patients with Cushing syndrome vs controls at baseline, including protein C (138 ± 41% vs 84 ± 25%, $P < .001$), protein S (94 ± 19% vs 74 ± 19%, $P = .001$), and antithrombin III (96 ± 18% vs 77 ± 13%, $P < .0001$). The 24-hour urinary free cortisol levels correlated positively with FVIII levels, $r = 0.43$, $P = .004$.

Conclusion Children with Cushing syndrome had elevated procoagulants, antifibrinolytics, and anticoagulants at baseline compared with controls; normalization of coagulation measures was seen after surgical cure. Despite the increase in anticoagulants, hypercortisolemia is associated with a hypercoagulable state in children, as is the case in adults. This finding has potential implications for prevention of venous thromboembolism in children with Cushing syndrome. *(J Pediatr 2016;177:227-31).*

Trial registration ClinicalTrials.gov: NCT00001595

Cushing syndrome is a state of excess glucocorticoids characterized by signs and symptoms such as obesity, striae, growth deceleration, and hypertension.[1] Cushing syndrome has been associated with hypercoagulability and thromboembolic events in adults. Data in pediatric patients are lacking.[2] In a study by Stuijver et al,[3] adults with Cushing syndrome were found to have a 10-fold increased risk of venous thromboembolism (VTE) compared with the normal population. In addition, this study showed a postoperative risk of VTE of 3.4% compared with 0% in patients who underwent operation for nonfunctional pituitary adenomas.

The hypercoaguable state in adults with Cushing syndrome is explained by enhanced coagulation factors and impaired fibrinolysis, as reflected by increased levels of fibrinogen, factor VIII (FVIII), von Willebrand factor (vWF), plasminogen activator inhibitor-1 (PAI-1), thrombin activatable fibrinolysis inhibitor, and α2-antiplasmin (A2AP).[4] The 2015 Endocrine Society clinical practice guidelines state that use of perioperative prophylaxis for VTE in adult patients with Cushing syndrome undergoing surgery may be useful and is indicated specifically for bedridden or low-mobility patients or those with urinary-free cortisol (UFC) levels greater than 5-fold normal.[5] No such guidelines, however, exist for children.

In this report, we describe 4 clinically significant thromboembolic events in children out of a total of 171 patients who underwent operation for Cushing syndrome at the National Institutes of Health (NIH) Clinical Center between 1997 and 2015. VTE is reported to occur in 0.07 of every 1000 children per year.[6,7] More recent studies have reported a greater prevalence of pediatric VTE, ranging from 4.9 to 21.9 VTE per 10 000 hospital admissions.[8,9] In comparison, the incidence of VTE in children after spinal fusion surgery is approximately 21 events per 10 000 spinal fusions per year.[10] Even when highest quoted

A2AP	α2-antiplasmin	NIH	National Institutes of Health
ACTH	Adrenocorticotropic hormone	PAI-1	Plasminogen activator inhibitor-1
ATIII	Antithrombin III	PTT	Partial thromboplastin time
BMI	Body mass index	UFC	Urinary-free cortisol
CRH	Corticotropin-releasing hormone	VTE	Venous thromboembolism
DVT	Deep-vein thrombosis	vWF	von Willebrand factor
FVIII	Factor VIII		

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VTE prevalence of 21.9 per 10 000 hospital admissions is used, the rate is significantly lower than the 4 of 171 pediatric patients with Cushing syndrome at the NIH who have experienced thromboembolic events ($P < .0001$). To better understand this, we prospectively evaluated several key coagulation elements in children with Cushing syndrome before and after surgical intervention to see whether these findings are consistent with those found in adults.

Methods

All patients were seen under 3 protocols (95CH0059, 97CH0076, and 00CH160) that treat children with Cushing syndrome at the NIH Clinical Research Center (ClinicalTrials.gov: NCT00001595). All protocols have been approved by the Institutional Review Board of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and all patients and/or their parents signed proper consent and/or assent forms.

Retrospective Data Analysis

One hundred seventy-one pediatric patients were treated for Cushing syndrome at the NIH Clinical Center between 1997 and 2015 (139 with adrenocorticotropic hormone [ACTH]-secreting pituitary tumors, 26 with primary adrenocortical Cushing syndrome, and 6 with ectopic ACTH- or corticotropin-releasing hormone [CRH]-secreting tumors). Four patients who had experienced a perioperative thromboembolic event were identified by electronic record review using the terms "thrombus," "clot," "deep-vein thrombosis (DVT)," and "embolism," "stroke," and "ischemia."

Prospective Study

Coagulation measures were obtained in 54 consecutive children (33 female and 21 male), mean age of 15.1 ± 3.9 years, who were admitted to the NIH for surgical intervention of confirmed Cushing syndrome between January 2013 through August 2015. Fifty-two of the patients with Cushing syndrome had a pituitary adenoma, 1 had an ectopic CRH and ACTH co-secreting adenoma, and 1 had an adrenal adenoma. Methods used to evaluate children for hypercortisolemia have been described previously.[11] Data also were collected from a control group (n = 18, 10 female, 8 male) of normocortisolemic children, mean age of 13.7 years, to use for comparison. Coagulation profiles were gathered on each patient before surgical intervention and at 6-12 months after surgery. Patients with Cushing syndrome underwent transsphenoidal surgery (n = 51), an adrenalectomy (n = 1), or removal of an ectopic ACTH-secreting pulmonary neuroendocrine tumor (n = 1). Coagulation profile included fibrinogen (reference range, 177-466 mg/dL), FVIII (41-184 IU/dL), vWF antigen (50-197 IU/dL), and PAI-1 plasma levels (3-86 IU/mL); antithrombin III (ATIII; 57-134%), protein C (59-144%), protein S (55-134%), and A2AP (75-132%) activities; and activated partial thromboplastin time (PTT) measurements (25.3-37.3 seconds).

Laboratory Methods

Antigen levels of FVIII, PAI-1, vWF:Ag, and fibrinogen were measured, whereas activity was measured for proteins C and S, A2AP, and ATIII. FVIII antigen levels were measured by correction of the activated partial thromboplastin time at various dilutions of patient sample mixed with FVIII-depleted plasma (George King Bio-Medical Inc, Overland Park, Kansas); vWF:Ag assays were done by immunoturbidometric measurements, fibrinogen measurements—by the method of Clauss; and protein C, protein S, ATIII, A2AP, and PAI-1 were analyzed by a chromogenic assays. All coagulation factors analyses were performed with a StaRevolution analyser (Diagnostica Stago Inc, Parsippany, New Jersey).

Statistical Analyses

Data were described with simple descriptive statistics and are presented as mean ± SD. Data were compared with *t* tests, or Wilcoxon rank-sum test, as appropriate, with SPSS 20 (IBM Inc, Armonk, New York). The relevant prevalence rates of VTE were compared with the z test for proportions. A 2-sided *P* value less than .05 was considered statistically significant.

Results

Retrospective Data Analysis: Identification of 4 Cases

Four children who had developed a perioperative thromboembolic event were identified. Case 1 was a 7-year-old girl who underwent transsphenoidal surgery. On postoperative day 6, she developed right shoulder pain with swelling around her central venous catheter line. An ultrasound scan detected an upper-extremity DVT in the right cephalic vein to the junction of the right subclavian vein. The central venous catheter was removed, and the patient was sent to the intensive care unit, where she was treated with unfractionated heparin and blood flow improved. Anticoagulation with low-molecular-weight heparin was continued 3 months after discharge. Follow-up at 6 months showed no residual pain or deficit.

The second case was a 16-year-old boy who underwent uncomplicated transsphenoidal surgery for removal of a pituitary adenoma. After uneventful recovery, he was discharged. Two weeks after surgery, he presented to the emergency department with persistent, severe headache and emesis. A computed tomography scan of the head revealed cerebral venous sinus thrombosis. He was admitted to the intensive care unit and was treated with enoxaparin therapy. Evaluation by hematology revealed an underlying factor V Leiden deficiency. At follow up 1-year after surgery, he had transitioned to daily aspirin therapy and had no residual sequelae.

The third case was a 13-year-old boy with a metastatic thymic ACTH- and CRH-secreting neuroendocrine tumor. The patient developed dyspnea and hypertension, despite treatment with several medications to lower blood pressure. He developed a clot at the site of a left internal jugular venous line and failed to respond to thrombolytic treatment twice; he was then placed on Lovenox (Sanofi US, Bridgewater, New Jersey) for