

Coagulation disorders in patients with abnormal serum cortisol level

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To the Editor: Cortisol is closely related to hemostasis.^[1] In patients with hyperadrenalism, that is, Cushing syndrome (CS), a reduction in the activated partial thromboplastin time (APTT), an increased level of coagulation factors, and an increased risk of thrombosis have been repeatedly reported.^[1,2] However, no studies reported the hemostatic status of patients with hypoadrenalism which is commonly seen in patients with pituitary diseases.

We undertook a retrospective study designed to evaluate the hemostatic status in patients with hypoadrenalism or hyperadrenalism. The study protocol was approved by the Ethics Review Board of Peking Union Medical College Hospital. All patients provided written informed consent to participate.

Clinical records of patients with pituitary adenomas were reviewed if they were hospitalized in the Department of Neurosurgery of our hospital from 2012 to 2018. In brief, the diagnosis of Cushing disease (CD) was based on the clinical symptoms and signs, magnetic resonance imaging, and hormone assays including low-dose and high-dose dexamethasone suppression test, inferior petrosal sinus sampling, and positive pathologically immunohistological staining for adrenocorticotropic hormone (ACTH). Patients with CD were considered as the hyperadrenalism group (hyperA). Non-functional pituitary adenoma (NF) was diagnosed based on normal endocrinological results and negative pathologically immunohistological staining. Patients with pituitary adenoma and pre-operative morning serum cortisol level (MSCL, at 08:00 AM) <138 nmol/L (5 µg/dL) were considered as the hypoadrenalism group (hypoA). Patients with NF and normal endocrinological results were considered as NF control group (NFC). Healthy people who underwent annual physical examination in our hospital in the same period were considered as the healthy control (HC). Participants were excluded if

they used any exogenous glucocorticoid (eg, hydrocortisone and prednisolone) 6 months before hospital admission or if they had no results of coagulation tests.

After hospital admission, blood was drawn at 08:00 AM for tests. Coagulation tests were evaluated using the Sysmex[®] CS-5100 Hemostasis system (Siemens Healthcare Diagnostics, Erlangen, Germany). The reference ranges of prothrombin time (PT), prothrombin activity, international normalized ratio (INR), APTT, thrombin time, and fibrinogen level were 10.4 to 12.6 s, 74.0% to 120.0%, 0.84 to 1.18, 22.7 to 31.8 s, 14.0 to 21.0 s, and 1.80 to 3.50 g/L, respectively, in our hemostasis laboratory. The serum cortisol, ACTH, insulin-like growth factor (IGF)-1 level, and thyroid function were evaluated using the direct chemiluminescent immunoassay method with the ADVIA Centaur[®] XP Immunoassay system or the IMMULITE[®] 2000 Immunoassay system (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). The standard deviation score of IGF-1 was calculated as follow = $[(X/M)^L - 1] / (L \times S)$, where X was an individual IGF-1 measurement, and L , M , and S were the age-specific parameters.

In total, 73 patients in hypoA group, 136 patients with CD (hyperA group), 124 patients in the NFC group, and 79 HCs were used for analysis. No participants had a history of coagulation disorders.

As shown in Supplementary Table 1, <http://links.lww.com/CM9/A604>, the mean age of patients with hypoA was 45.0 years, and 30.1% were females. The systolic pressure of hypoA was similar to that of HC, significantly lower than that of NFC ($P = 0.002$), while no difference was found in diastolic pressure between hypoA and NFC or HC. As for liver function tests, there was a difference between patients with hypoA and HC in alanine transaminase (ALT), aspartate transaminase, albumin, and alkaline phosphatase.

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Table 1: Results of coagulation tests of all participants.

Items	HC	NFC	hypoA	hyperA
APTT (s)	28.1 (25.4–29.7)	26.3 (24.4–28.5)	33.6 (31.2–37.3) ^{**,†††}	23.3 (20.7–25.3) ^{**,†††}
PT (s)	11.6 (11.2–12.2)	11.5 (11.1–11.8)	12.1 (11.4–12.5) ^{**,†††}	11.1 (10.7–11.5) ^{**,†††}
PTA (%)	96.5 ± 9.0	102.1 ± 11.2 [*]	90.6 ± 9.6 ^{**,†††}	107.2 ± 13.5 ^{**,†††}
INR	0.988 ± 0.058	0.970 ± 0.056	1.034 ± 0.079 ^{**,†††}	0.956 ± 0.060 [*]
TT (s)	17.9 (17.3–18.8)	17.7 (17.3–18.5)	18.1 (17.4–19.2)	18.1 (17.3–18.8)
Fbg (g/L)	2.51 (2.15–2.93)	2.83 (2.54–3.22) ^{**}	3.02 (2.47–3.41) ^{**}	2.83 (2.54–3.80) [†]

Data are expressed as mean ± standard deviation or median (interquartile range). ^{*}*P* < 0.01, ^{**}*P* < 0.001 when compared with HC using Tukey *post hoc* test or Dunn *post hoc* tests. [†]*P* < 0.05, ^{††}*P* < 0.01, ^{†††}*P* < 0.001 when comparing with NF. APTT: Activated partial thromboplastin time; HC: Healthy control; hyperA: Hyperadrenalism group; hypoA: Hypoadrenalism group; INR: International normalized ratio; IQR: Interquartile range; PT: Prothrombin time; PTA: Prothrombin activity; NF: Non-functional pituitary adenoma; NFC: NF control group; SD: Standard deviation; TT: Thrombin time.

tase. However, the value of liver function tests of most of the patients was in the reference range.

Supplementary Table 2, <http://links.lww.com/CM9/A604> indicated the endocrinological results of patients. Since HC did not need endocrinological evaluation in the annual physical examination, hypoA or hyperA were compared with NFC. As expected, the MSCL and ACTH were significantly higher in hyperA (both *P* < 0.001) and lower in hypoA (*P* < 0.001 for MSCL, *P* = 0.002 for ACTH). Free triiodothyronine (*P* = 0.001), thyroxine (T4, *P* < 0.001), free thyroxine (*P* < 0.001), and IGF-1 (*P* = 0.002) in patients with hypoA were significantly lower than that in patients with NF.

Table 1 indicated the results of coagulation tests. A significant difference was found in PT, INR, and APTT among HC, NFC, hypoA, and hyperA (*P* < 0.001). PT, INR, and APTT were all significantly prolonged in patients with hypoA than that in HC (for PT, median = 12.1 *vs.* 11.6 s, *P* = 0.004; for INR, median = 1.034 *vs.* 0.988, *P* < 0.001; for INR for APTT, median = 33.6 *vs.* 28.1 s, *P* < 0.001) and were significantly shorter in patients with hyperA (all *P* < 0.001), while no significant difference in PT, INR, or APTT was found between patients with NFC and HC [Supplementary Figure 1, <http://links.lww.com/CM9/A604>].

Considering the sample size and the results of pairwise analyses, we chose APTT, PT, ALT, albumin, T4, gender, and age for multivariable logistic regression with forward stepwise (likelihood ratio) method, using NFC as reference category. Logistic regression analysis showed that longer APTT (odds ratio [OR] = 1.761, 95% confidence interval [CI] = 1.439–2.156, *P* < 0.001), younger (OR = 0.945, 95% CI = 0.907–0.985, *P* = 0.008), lower albumin (OR = 0.746, 95% CI = 0.627–0.887, *P* = 0.001), and lower T4 (OR = 0.635, 95% CI = 0.483–0.834, *P* = 0.001) were associated with hypoA, while shorter APTT (OR = 0.474, 95% CI = 0.291–0.772, *P* = 0.003), younger (OR = 0.719, 95% CI = 0.591–0.874, *P* = 0.001), lower albumin (OR = 0.484, 95% CI = 0.324–0.729, *P* < 0.001), lower T4 (OR = 0.524, 95% CI = 0.297–0.924, *P* = 0.03), higher ALT (OR = 1.075, 95% CI = 1.013–1.141, *P* = 0.02), and female (OR = 90.4, 95% CI = 3.57–2288, *P* = 0.006) were associated with hyperA [Supplementary Table 3, <http://links.lww.com/CM9/A604>].

Our study analyzed the hemostatic disorders in patients with hypoadrenalism for the first time, indicating that both APTT and PT were significantly prolonged in hypoA and were significantly shortened in patients with CD.

Previous studies (*in vitro* or *in vivo*) exploring the hemostatic abnormalities in hypoA are lacking.^[1] However, there were some studies on hypercortisolism, such as CS, which might provide clues about the effect of cortisol on coagulation. Most of those studies have indicated that the levels of components in the coagulation cascade are increased significantly in CS, especially factors VIII and IX.^[2–4] A reduction of APTT in CS has been described repeatedly,^[1–4] which might be the outcome of an increased level of factors VIII and IX. Besides, Brotman *et al*^[5] showed that healthy volunteers who took dexamethasone (per os) for 5 days had significantly higher levels of factors VII, VIII, XI, and fibrinogen. Our study found a significantly decreased APTT and PT in patients with CD, comparing with NFC or HC, which was consistent with previous studies. These results could be extrapolated to suggest that patients with hypoA would have lower levels of factors VIII and IX, leading to an increase in APTT.

This was a rare study to assess coagulation abnormalities in patients with hypoadrenalism, which may have several potential clinical implications. For example, APTT might be used to monitor the dosage of glucocorticoid replacement therapy (GRT) in patients with hypoadrenalism. Although GRT is recommended and used widely for the treatment of hypoadrenalism, an accurate monitor for the glucocorticoid dose is lacking. In GRT, short-acting glucocorticoids such as hydrocortisone and prednisolone are the main choices; thus, the MSCL is not an accurate way to monitor the glucocorticoid dose. Nowadays, the glucocorticoid dose is adjusted to ascertain the optimal glucocorticoid dose based primarily on the experience of the treating physician. Our results indicated that APTT might be useful to monitor the dose of glucocorticoids in GRT. An increased APTT indicates an insufficient dose of the glucocorticoid, whereas a decreased APTT indicates overuse of the glucocorticoid. However, further studies are needed to confirm the clinical value of APTT in monitoring the glucocorticoid dose.

In conclusion, coagulation disorders are found in patients with hypoA or hyperA mainly in the intrinsic pathways. APTT is significantly prolonged in hypoA and shortens in hyperA, which might have potential clinical implications.

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Conflicts of interest

None.

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