ACTH-cortisol dissociation in patients with Kawasaki disease: a retrospective study

Keiko Aso and Mari Satoh

Department of Pediatrics, Toho University Omori Medical Center, Ota-ku, Tokyo 143-8541, Japan

Abstract. ACTH-cortisol dissociation is recognized in patients with critical illnesses. Cytokines, including tumor necrosis factor-α and interleukin-6 induce hypercortisolemia by enhancing the ACTH-independent synthesis and secretion of cortisol and by reducing cortisol breakdown. Subsequently, hypercortisolemia suppresses ACTH secretion by negative feedback inhibition. ACTH-cortisol dissociation in patients with systemic inflammatory diseases has not been reported. Here, we examined whether ACTH-cortisol dissociation is recognized in patients with Kawasaki disease (KD) associated with hypercytokinemia, as well as the possible cytokine involvement in ACTH-cortisol dissociation, retrospectively. The levels of serum cortisol, plasma ACTH, and cytokine-induced proteins, *i.e.*, plasma C-reactive protein (CRP), serum ferritin, and urinary β2-microglobulin (U-β2MG), in 232 patients with KD were measured at diagnosis. Quartile groups based on cytokine-induced protein levels were formed (Q1, Q2, Q3, and Q4). We found a low median plasma ACTH [median (range): 8.9 (<2.0–332.0) pg/mL] but a high median serum cortisol level [median (range): 25.8 (1.4–99.8) μg/dL] in the entire study population. The median serum cortisol levels were significantly higher in the CRP-Q4, ferritin-Q4, and U-β2MG-Q4 groups than in the CRP-Q1, ferritin-Q2, and U-β2MG-Q1 groups, respectively ($p < 0.01$; $p < 0.01$; $p < 0.001$). The median plasma ACTH levels were significantly lower in the CRP-Q4 and ferritin-Q4 groups than in the CRP-Q1 and ferritin-Q1 groups, respectively ($p < 0.001$; $p < 0.001$). ACTH-cortisol dissociation was identified in patients with KD. Our findings suggest that inflammatory cytokines are involved in ACTH-independent hypercortisolemia in patients with KD. ACTH-cortisol dissociation in other systemic inflammatory diseases needs further investigation.

Key words: Cortisol, ACTH, Cytokine, Kawasaki disease, ACTH-cortisol dissociation

---

HYPERCORTISOLEMIA in patients with critical illnesses has traditionally been attributed to stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis and increased ACTH-driven cortisol synthesis and secretion [1]. However, low plasma ACTH levels have been reported in patients with a critical illness in the presence of elevated circulating cortisol levels [2], called the "ACTH-cortisol dissociation." Cytokines, neuro-transmitters, and neuropeptides are reported to be involved in ACTH-independent hypercortisolemia [2, 3]. Subsequently, elevated serum cortisol levels suppress plasma ACTH secretion *via* negative feedback inhibition. Cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-6, cause ACTH-independent hyper-cortisolemia by increased adrenocortical synthesis and secretion of cortisol and by reduced cortisol metabolism [4].

Kawasaki disease (KD) is an acute systemic vasculitis that mainly affects infants and children and can lead to serious complications, such as coronary artery dilatation and aneurysm. Although its pathogenesis remains unknown, KD is one of the systemic inflammatory diseases. Systemic inflammatory diseases are caused by excessive inflammatory cytokine production due to defective inflammatory regulation in innate immunity, *e.g.*, systemic onset juvenile idiopathic arthritis and periodic fever syndrome [5]. Some patients with systemic inflammatory diseases may be critically ill. Studies on ACTH-cortisol dissociation in patients with systemic inflammatory diseases are lacking.

Various inflammatory cytokines, such as TNF-α, IL-1, IL-2, IL-6, and interferon (INF)-γ, are elevated in patients with KD [5, 6]. C-reactive protein (CRP), ferritin, and β2-microglobulin (β2MG) are cytokine-induced proteins and they reflect the expression of IL-6, TNF-α, and INF-γ, respectively [7-9]. Furthermore, in our previous study on serum cortisol levels in children without known adrenal dysfunction during an acute illness [10], a patient with KD whose serum cortisol level was high at diagnosis, suffered from heart failure. High

serum cortisol level [11-13] and low ACTH/cortisol ratio [14] have been reported to be associated with adverse outcomes or high mortality in patients with several diseases. Therefore, the levels of cytokine-induced proteins, cortisol, and ACTH have been used as indexes for determining the severity of KD at the Toho University Omori Medical Center in recent years.

Here, we assessed ACTH-cortisol dissociation in patients with KD associated with hypercytokinemia and evaluated the association between ACTH-cortisol dissociation and cytokine-induced proteins, retrospectively.

Materials and Methods

Study population

Four hundred and forty-six patients with KD who required intravenous immunoglobulin therapy were admitted to the Toho University Omori Medical Center from January 2014 to December 2019. KD diagnosis was based on the criteria of the Diagnostic Guidelines for KD (the 5th revised edition) [15]. We included patients with KD whose serum cortisol and plasma ACTH levels could be obtained because they were diagnosed between 0900 h and 1700 h. We excluded patients with concomitant medical disorders (pituitary, adrenal, or renal diseases) and those who had received steroids. This study was approved by the Ethics Committee of the Toho University Omori Medical Centre (approval no. M20029 18254 16202). The need for informed consent was waived in view of the retrospective study design.

Study design

Blood sampling *via* venipuncture and urinary sampling was performed at the time of KD diagnosis between 0900 h and 1700 h. The plasma CRP, serum ferritin, serum cortisol, plasma ACTH, and urinary β2MG (U-β2MG) levels were measured. Considering the reported loss of circadian and ultradian rhythms during an acute illness [16-18], serum cortisol and plasma ACTH levels might not be influenced by clock-time in patients with KD.

Patients were classified into mild (<5 points) and severe (≥5 points) groups based on the KD scoring system for the prediction of non-responsiveness to initial intravenous immunoglobulin therapy [19]. The variables in this system included days of illness at initial treatment, chronological age, neutrophil percentage, platelet count, and the plasma levels of sodium, aspartate aminotransferase, and CRP. Plasma CRP, serum ferritin, U-β2MG, serum cortisol, and plasma ACTH levels in the mild and severe groups were compared.

Patients were categorized into quartile groups according to the plasma CRP, serum ferritin, and U-β2MG levels. The first, second, third, and fourth quartile groups were named Q1, Q2, Q3, and Q4, respectively. The serum cortisol and plasma ACTH levels were compared among these quartile groups.

Plasma CRP, serum ferritin, U-β2MG, and serum cortisol levels were compared between patients whose ACTH levels were below the test sensitivity level of 2.0 pg/mL (undetectable ACTH group) and those with ACTH levels ≥2.0 pg/mL (detectable ACTH group).

U-β2MG generally tends to decrease at a urinary pH <5.5 [20]. We therefore excluded the patients with a urinary pH <5.5 from the U-β2MG analysis.

Assays

Serum cortisol levels were measured using an electro-chemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany) with a sensitivity of 0.054 μg/dL and the intra- and inter-assay coefficients of variability of <15% and <10%, respectively, at two different concentrations. The plasma ACTH levels were measured using an electro-chemiluminescence immunoassay (Roche Diagnostics GmbH) with a sensitivity of 1.0 pg/mL and the intra- and inter-assay coefficients of variability of <10% and <25%, respectively, at two different concentrations. Plasma CRP levels were measured using a latex immunoassay (Eiken Kagaku Co., Ltd., Tochigi, Japan), whereas plasma ferritin levels were measured using an electro-chemiluminescence immunoassay (Roche Diagnostics GmbH). U-β2MG levels were measured using a latex immunoassay (Nittobo Medical Co., Ltd., Fukushima, Japan).

Statistical analysis

All statistical analyses were performed using the StatMate V software (ATMS Co., Ltd., Tokyo, Japan). Plasma ACTH levels with a sensitivity <2.0 pg/mL were replaced with 2.0 pg/mL during analysis. The chi-squared test was used for the categorical analysis. The Mann–Whitney *U* test was used to determine the differences between two groups, whereas the Kruskal–Wallis H test was used to determine the differences among four groups, followed by a Dunn's *post hoc* test. $p < 0.05$ was considered statistically significant. All data are expressed as median (range), except for the undetectable ACTH value.

Results

Characteristics of patients with KD

Of the 446 patients, 232 patients (131 males and 101 females) whose serum cortisol and plasma ACTH levels could be obtained were included in the study. The median age at the time of KD diagnosis was 2.3 (0.2–

8.6) yr. Moreover, the patients were diagnosed by day 4.0 (1.0–12.0) of the illness; of note, a majority of the 221 patients (95.3%) was diagnosed between days 2.0 and 6.0 of the illness. No patient had a coronary aneurysm. The median plasma ACTH level was low at 8.9 (<2.0–332.0) pg/mL, whereas the median serum cortisol level was high at 25.8 (1.4–99.8) μg/dL. Thirty-five patients (15.1%) had plasma ACTH levels <2.0 pg/mL. The median plasma ACTH and serum cortisol levels did not show significant differences based on the days of the illness at the time of diagnosis (2.0–6.0 days). U-β2MG levels were analyzed in 170 patients (73.3%).

Serum cortisol, plasma ACTH, and cytokine-induced protein levels in terms of KD severity

The clinical characteristics of patients in the mild and severe groups are listed in Table 1. One hundred and sixty-five patients were classified into the mild group (71.1%), and sixty-seven patients into the severe group (28.9%). The median age in the severe group was significantly higher than that in the mild group [3.2 (0.3–8.2) vs. 2.0 (0.2–8.6) yr, $p = 0.003$]. The median serum cortisol level in the severe group was significantly higher than that in the mild group [30.6 (2.0–99.8) μg/dL vs. 24.1 (1.4–65.2) μg/dL, $p < 0.001$]. In contrast, the median plasma ACTH level in the severe group was significantly lower than that in the mild group [6.3 (<2.0–107.0) vs. 11.1 (<2.0–332.0) pg/mL, $p = 0.003$]. The median plasma CRP, serum ferritin, and U-β2MG levels in the severe group were significantly higher than those in the mild group [8.0 (0.0–26.4) vs. 4.9 (0.1–23.2) mg/dL, 195.3 (37.6–802.8) vs. 126.0 (16.5–536.3) ng/mL, and 2,393.0 (90.0–102,621.0) vs. 372.0 (0.0–40,314.0) μg/L, respectively, $p < 0.001$].

Among the 35 patients with undetectable ACTH, 19 patients were classified as mild, whereas 16 patients were classified as severe. The percentage of the patients with undetectable ACTH was significantly higher in the severe group than in the mild group (23.9% vs. 11.5%; $p = 0.026$).

Serum cortisol and plasma ACTH levels in the quartile groups according to the cytokine-induced protein levels

The patients were stratified into quartile groups ($n = 58$ per group) according to the levels of plasma CRP (mg/dL) as follows: Q1, <3.8; Q2, 3.8–6.1; Q3, 6.1–8.9; and Q4, >8.9. The median serum cortisol levels were significantly higher in Q3 and Q4 than in Q1 [29.2 (4.8–78.1) and 26.6 (2.0–99.8) vs. 20.0 (1.4–52.2) μg/dL, $p < 0.01$] (Fig. 1a). The median plasma ACTH level was significantly lower in Q4 than in Q1 [6.3 (<2.0–106.0) vs. 16.9 (<2.0–190.0) pg/mL, $p < 0.001$] (Fig. 1b).

The patients were stratified into quartile groups ($n = 58$ per group) according to the serum ferritin levels (ng/mL) as follows: Q1, <99.1; Q2, 99.1–142.6; Q3, 142.6–195.0; and Q4, >195.0. The median serum cortisol level in Q4 was significantly higher than that in Q2 [27.4 (6.4–82.7) vs. 21.1 (1.4–78.1) μg/dL, $p < 0.01$] (Fig. 1c). The median plasma ACTH level in Q4 was significantly lower than that in Q3 and Q1 [5.8 (<2.0–89.9) vs. 10.4 (<2.0–247.0) and 21.0 (<2.0–190.0) pg/mL, $p < 0.05$ and $p < 0.001$, respectively], while that in Q2 [8.5 (<2.0–332.0) pg/mL] was significantly lower than that in Q1 ($p < 0.05$) (Fig. 1d).

Further, the patients were stratified into quartile groups according to the U-β2MG levels (μg/L) as follows: Q1, <221.5, $n = 43$; Q2, 221.5–606.5, $n = 42$; Q3, 606.5–2,909.3, $n = 42$; and Q4, >2,909.3, $n = 43$. The median serum cortisol level in Q4 [34.6 (15.7–99.8)

**Table 1** Comparisons in terms of severity of Kawasaki disease ($n = 232$)

	Mild ($n = 165$)	Severe ($n = 67$)	p value
Ratio of male to female	98:67	33:34	0.158
Age (yr)	2.0 (0.2–8.6)	3.2 (0.3–8.2)	0.003
CRP (mg/dL)	4.9 (0.1–23.2)	8.0 (0.0–26.4)	<0.001
Ferritin (ng/mL)	126.0 (16.5–536.3)	195.3 (37.3–802.8)	<0.001
U-β2MG (μg/L)	372.0 (0.0–40,314.0)[a]	2,393.0 (90.0–102,621.0)[b]	<0.001
Cortisol (μg/dL)	24.1 (1.4–65.2)	30.6 (2.0–99.8)	<0.001
ACTH (pg/mL)	11.0 (<2.0–332.0)	6.3 (<2.0–107.0)	0.003
undetectable ACTH number (%)	19 (11.5)	16 (23.9)	0.026

All data are expressed as median (range), except for undetectable ACTH number.
Abbreviations: CRP, C-reactive protein; U-β2MG, urinary β2-microglobulin.
[a] $n = 117$
[b] $n = 53$
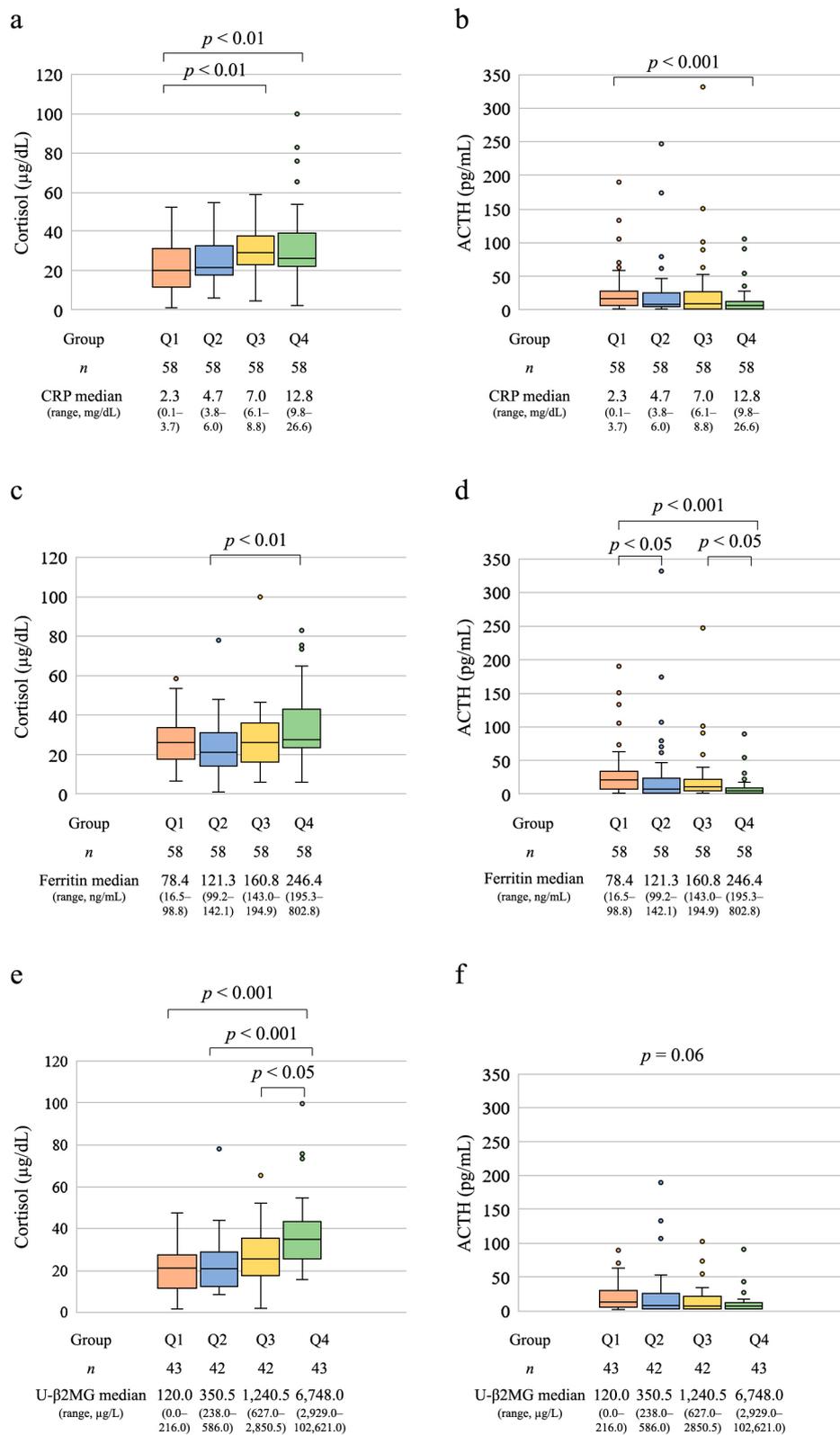
Fig. 1 Serum cortisol and plasma ACTH levels in the quartile groups according to the cytokine-induced proteins levels.

(a and b) Plasma CRP, (c and d) serum ferritin, and (e and f) U-β2MG levels. Q1, Q2, Q3, and Q4 represent the first, second, third, and fourth quartile groups, respectively. The boxes represent the medians and interquartile ranges. The whiskers represent 1.5 times the interquartile range of the data. White dots represent outliers. Data were compared using the Kruskal–Wallis H test followed by a Dunn's post hoc for variables. $p < 0.05$ was considered statistically significant. CRP, C-reactive protein; U-β2MG, urinary β2-microglobulin.

μg/dL] was the highest among all groups and showed statistical significance [*vs.* Q3: 25.4 (2.0–65.2), *p* < 0.05; *vs.* Q2: 20.6 (8.5–78.1), *p* < 0.001; and *vs.* Q4: 21.0 (1.4–47.6), *p* < 0.001] (Fig. 1e). There was no significant difference in the median plasma ACTH levels between the four groups [Q1: 12.3 (<2.0–89.9), Q2: 7.7 (<2.0–190.0), Q3: 6.6 (<2.0–102.0), and Q4: 6.5 (<2.0–90.4) pg/mL, *p* = 0.06] (Fig. 1f).

Cytokine-induced proteins and serum cortisol levels in terms of plasma ACTH levels

The median levels of plasma CRP and serum ferritin in the patients with undetectable ACTH were significantly higher than those in patients with detectable ACTH [plasma CRP: 7.6 (0.9–20.6) *vs.* 5.6 (0.1–26.4) mg/dL, *p* = 0.003; and serum ferritin: 156.1 (52.8–536.3) *vs.* 140.7 (16.5–802.8) ng/mL, *p* = 0.044] (Table 2). There was no significant difference in terms of the median U-β2MG and serum cortisol levels between the undetectable ACTH and detectable ACTH groups [U-β2MG: 1,027.5 (64.0–28,333.0) *vs.* 549.0 (0.0–102,621.0) μg/L, *p* = 0.251; and serum cortisol: 23.8 (1.4–82.7) *vs.* 26.1 (2.0–99.8) μg/dL, *p* = 0.225].

Discussion

In patients with KD, we identified ACTH-cortisol dissociation, *i.e.*, a low median plasma ACTH level in the presence of a high median serum cortisol level. To the best of our knowledge, this is the first study reporting ACTH-cortisol dissociation in patients with systemic inflammatory diseases. Moreover, our findings suggest that inflammatory cytokines were involved in ACTH-independent hypercortisolemia in patients with KD. In the severe group with higher levels of cytokine-induced proteins than that in the mild group, the median serum cortisol level was significantly higher, but the median plasma ACTH level was significantly lower compared with those in the mild group. The median serum cortisol

levels were significantly higher in the high-CRP, high-ferritin, and high-U-β2MG groups than in the low-CRP, low-ferritin, and low-U-β2MG groups, respectively. The median plasma ACTH levels were significantly lower in the high-CRP and high-ferritin groups than in the low-CRP and low-ferritin groups, respectively.

Boonen *et al.* have reported that inflammatory cytokines, including TNF-α and IL-6, are positively correlated with cortisol production, and that cortisol clearance is reduced by the suppression of 11β-HSD2 activity, which catalyzes the conversion of cortisol to inactivated cortisone in critically ill patients [4]. TNF-α, IL-1, and IL-6 have been reported to enhance steroidogenesis in the human adrenocortical cell line NCI-H295R [21-23]. In contrast, TNF-α has been observed to suppress the activity of 11β-HSD2 in the porcine renal epithelial cell line LLC-PK$_1$ [24], and the mRNA expression of key proinflammatory cytokines (TNF-α, IL-1β, and IL-6) has been shown to be upregulated but that of 11β-HSD2 downregulated in the colon tissue from patients with inflammatory bowel disease [25]. Therefore, we speculated that the ACTH-independent hypercortisolemia in patients with KD was due to the increase in synthesis and secretion of cortisol and to the reduction in cortisol clearance by inflammatory cytokines.

The low plasma ACTH levels in patients with KD are presumed to be caused by the negative feedback inhibition of hypercortisolemia. In this study, the plasma ACTH levels in 15.1% of the patients were less than the test sensitivity level of 2.0 pg/mL, which are extremely low compared with the levels reported in previous studies on ACTH-cortisol dissociation [4, 26, 27]. The inflammatory cytokine levels are suggested to be higher in the undetectable ACTH group than those in the detectable ACTH group because the levels of the cytokine-induced proteins in the undetectable ACTH group were significantly higher than those in the detectable ACTH group. Therefore, in patients with KD, it is the inflammatory cytokines, not the ACTH, that may

Table 2 Cytokine-induced proteins and serum cortisol levels in terms of plasma ACTH levels

	ACTH		*p* value
	undetectable (*n* = 35)	detectable (*n* = 197)	
CRP (mg/dL)	7.6 (0.9–20.6)	5.6 (0.1–26.4)	0.003
Ferritin (ng/mL)	156.1 (52.8–536.3)	140.7 (16.5–802.8)	0.044
U–β2MG (μg/L)	1,027.5 (64.0–28,333.0)[a]	549.0 (0.0–102,621.0)[b]	0.251
Cortisol (μg/dL)	23.8 (1.4–82.7)	26.1 (2.0–99.8)	0.225

All data are expressed as median (range).
Abbrevations: CRP, C-reactive protein; U-β2MG, urinary β2-microglobulin.
[a] *n* = 30
[b] *n* = 140

have remarkably contributed to synthesis and secretion of cortisol.

The sustained lack of ACTH secretion in patients with prolonged critical illnesses has been reported to be caused by the loss of zonational structure, lipid depletion, and reduced ACTH-related gene expression, thus contributing to adrenal insufficiency [28]. The sustained HPA axis suppression has also been reported in a high proportion of patients with KD treated with intravenous immunoglobulin and prednisolone, despite the rather short treatment duration and relatively small amounts of administered glucocorticoids [29]. Although we did not study the chronological changes in the serum cortisol and plasma ACTH levels after the treatment, the ACTH-cortisol dissociation might be associated with prolonged HPA axis suppression. It is thus necessary to investigate the HPA axis function after treatment in patients with KD.

Nonetheless, there were several limitations in our study. First, although the association between the levels of cytokine-induced proteins and ACTH-cortisol dissociation was investigated, the levels of inflammatory cytokines themselves were not measured. Therefore, a prospective investigation of the ACTH-cortisol dissociation and levels of inflammatory cytokines is needed. Second, comparison of the chronological age and plasma CRP levels between the mild and severe groups was biased because these were the headings of the KD-severity scoring. However, the comparison among the quartile groups and that between the undetectable and detectable ACTH groups suggested the involvement of cytokines in ACTH-cortisol dissociation in patients with KD.

In conclusion, we identified ACTH-cortisol dissociation in patients with KD, suggesting that inflammatory cytokines may be involved in ACTH-independent hypercortisolemia. However, ACTH-cortisol dissociation in other systemic inflammatory diseases needs to be investigated in future studies.

Acknowledgments

Disclosure

None of the authors have any potential conflicts of interest associated with this research.

References

1. Vermes I, Beishuizen A (2001) The hypothalamic-pituitary-adrenal response to critical illness. *Best Pract Res Clin Endocrinol Metab* 15: 495–511.
2. Vermes I, Beishuizen A, Hampsink RM, Haanen C (1995) Dissociation of plasma adrenocorticotropin and cortisol levels in critically ill patients: possible role of endothelin and atrial natriuretic hormone. *J Clin Endocrinol Metab* 80: 1238–1242.
3. Bornstein SR, Chrousos GP (1999) Clinical review 104: adrenocorticotropin (ACTH)- and non-ACTH-mediated regulation of the adrenal cortex: neural and immune inputs. *J Clin Endocrinol Metab* 84: 1729–1736.
4. Boonen E, Vervenne H, Meersseman P, Andrew R, Mortier L, *et al.* (2013) Reduced cortisol metabolism during critical illness. *N Engl J Med* 368: 1477–1488.
5. Yokota S, Kikuchi M, Nozawa T, Kanetaka T, Sato T, *et al.* (2015) Pathogenesis of systemic inflammatory diseases in childhood: "lessons from clinical trials of anti-cytokine monoclonal antibodies for Kawasaki disease, systemic onset juvenile idiopathic arthritis, and cryopyrin-associated periodic fever syndrome." *Mod Rheumatol* 25: 1–10.
6. Abe J (2017) Immunological abnormalities and use of biomarkers and cytokines to predict the severity of Kawasaki disease. In: Saji BT, Newburger JW, Burns JC, Takahashi M (eds) Kawasaki Disease. Springer Nature Switzerland AG, Basel, Switzerland: 31–37.
7. Fleck A (1989) Clinical and nutritional aspects of changes in acute-phase proteins during inflammation. *Proc Nutr Soc* 48: 347–354.
8. Tran TN, Eubanks SK, Schaffer KJ, Zhou CY, Linder MC (1997) Secretion of ferritin by rat hepatoma cells and its regulation by inflammatory cytokines and iron. *Blood* 90: 4979–4986.
9. Grönberg A, Kiessling R, Fiers W (1985) Interferon-gamma is a strong modulator of NK susceptibility and expression of beta 2-microglobulin but not of transferrin receptors. *Cell Immunol* 95: 195–202.
10. Aso K, Sato M, Saji T, Hasegawa Y (2013) Glucocorticoid replacement therapy in children with hypoadrenalism during physiological stress. Program of 9th Joint Meeting of Paediatric Endocrinology, ESPE-PES-APEG-APPES-ASPAE-JSPE-SLEP, P1-d1-237 (Abstract).
11. Sam S, Corbridge TC, Mokhlesi B, Comellas AP, Molitch ME (2004) Cortisol levels and mortality in severe sepsis. *Clin Endocrinol* 60: 29–35.
12. Christ-Crain M, Stolz D, Jutla S, Couppis O, Müller C, *et al.* (2007) Free and total cortisol levels as predictors of severity and outcome in community-acquired pneumonia. *Am J Respir Crit Care Med* 176: 913–920.
13. Zi WJ, Shuai J (2013) Cortisol as a prognostic marker of short-term outcome in chinese patients with acute ische-

mic stroke. *PLoS One* 8: e72758.

14. Lesur O, Roussy JF, Chagnon F, Gallo-Payet N, Dumaine R, *et al.* (2010) Proven infection-related sepsis induces a differential stress response early after ICU admission. *Crit Care* 14: R131.

15. Ayusawa M, Sonobe T, Uemura S, Ogawa S, Nakamura Y, *et al.* (2005) Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). *Pediatr Int* 47: 232–234.

16. Peeters B, Langouche L, Van den Berghe G (2017) Adrenocortical stress response during the course of critical illness. *Compr Physiol* 8: 283–298.

17. Spiga F, Lightman SL (2015) Dynamics of adrenal glucocorticoid steroidogenesis in health and disease. *Mol Cell Endocrinol* 408: 227–234.

18. Nickels DA, Moore DC (1989) Serum cortisol responses in febrile children. *Pediatr Infect Dis J* 8: 16–20.

19. Kobayashi T, Inoue Y, Takeuchi K, Okada Y, Tamura K, *et al.* (2006) Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation* 113: 2606–2612.

20. Hibi Y, Uemura O, Nagai T, Yamakawa S, Yamasaki Y, *et al.* (2015) The ratios of urinary β2-microglobulin and NAG to creatinine vary with age in children. *Pediatr Int* 57: 79–84.

21. Mikhaylova IV, Kuulasmaa T, Jääskeläinen J, Voutilainen R (2007) Tumor necrosis factor-alpha regulates steroidogenesis, apoptosis, and cell viability in the human adrenocortical cell line NCI-H295R. *Endocrinology* 148: 386–392.

22. Tkachenko IV, Jääskeläinen T, Jääskeläinen J, Palvimo JJ, Voutilainen R (2011) Interleukins 1α and 1β as regulators of steroidogenesis in human NCI-H295R adrenocortical cells. *Steroids* 76: 1103–1115.

23. Strickland J, McIlmoil S, Williams BJ, Seager DC, Porter JP, *et al.* (2017) Interleukin-6 increases the expression of key proteins associated with steroidogenesis in human NCI-H295R adrenocortical cells. *Steroids* 119: 1–17.

24. Heiniger CD, Rochat MK, Frey FJ, Frey BM (2001) TNF-alpha enhances intracellular glucocorticoid availability. *FEBS Lett* 507: 351–356.

25. Hussey M, Holleran G, Smith S, Sherlock M, McNamara D (2017) The role and regulation of the 11 beta-hydroxysteroid dehydrogenase enzyme system in patients with inflammatory bowel disease. *Dig Dis Sci* 62: 3385–3390.

26. Raff H, Biru N, Reisinger N, Kramer DJ (2017) Dissociation of ACTH and cortisol in septic and non-septic ICU patients. *Endocrine* 55: 307–310.

27. Michalaki M, Margeli T, Tsekouras A, Gogos CH, Vagenakis AG, *et al.* (2010) Hypothalamic-pituitary-adrenal axis response to the severity of illness in non-critically ill patients: does relative corticosteroid insufficiency exist? *Eur J Endocrinol* 162: 341–347.

28. Boonen E, Langouche L, Janssens T, Meersseman P, Vervenne H, *et al.* (2014) Impact of duration of critical illness on the adrenal glands of human intensive care patients. *J Clin Endocrinol Metab* 99: 4214–4222.

29. Goto M, Miyagawa N, Kikunaga K, Miura M, Hasegawa Y (2015) High incidence of adrenal suppression in children with Kawasaki disease treated with intravenous immunoglobulin plus prednisolone. *Endocr J* 62: 145–151.