Clin Pediatr Endocrinol 2015; 24(3), 69–75


## Original Article

# Single serum cortisol values at 09:00 h can be indices of adrenocortical function in children with Kawasaki disease treated with intravenous immunoglobulin plus prednisolone

Masahiro Goto[1], Naoyuki Miyagawa[2, 4], Kaori Kikunaga[2], Masaru Miura[3], and Yukihiro Hasegawa[1, 2]

[1]*Division of Endocrinology and Metabolism, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan*

[2]*Department of General Pediatrics, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan*

[3]*Division of Cardiology, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan*

[4]*Division of Hematology, Kanagawa Children's Medical Center, Yokohama, Japan*

**Abstract.** Combination treatment with intravenous immunoglobulin (IVIG) plus prednisolone is effective for prevention of cardiovascular complications in children with Kawasaki disease (KD). However, administration of prednisolone for approximately 20 d in this regimen causes adrenocortical suppression in a high proportion of treated children. To establish a simple method to screen for this suppression, we performed a prospective study on 72 children with KD treated with this regimen in our institution from February 2012 to March 2014. By performing ROC analysis of 21 initial patients treated between February and June 2012, a serum cortisol value at 09:00 h of 5 mcg/dL was established as a threshold for intact adrenocortical function, which is equivalent to a peak serum cortisol value of higher than 15 mcg/dL in the CRH stimulation test. Then, we applied this screening test to 51 subsequent patients treated between July 2012 and March 2014. Approximately 90% of the patients with morning serum cortisol values above 5 mcg/dL 2 to 6 mo after the cessation of initial prednisolone treatment had peak serum cortisol values exceeding 15 mcg/dL, suggesting the efficacy of this approach.

**Key words:** screening, adrenal function, Kawasaki disease, prednisolone

## Introduction

A newly designed regimen of combination treatment with intravenous immunoglobulin (IVIG) plus prednisolone is effective for prevention of cardiovascular complications in children with Kawasaki disease (KD). It significantly reduces coronary artery complications in patients with high risk scores for IVIG unresponsiveness (1, 2). Because of this favorable outcome, the number of children treated with this regimen is expected to increase.

Received: December 29, 2014
Accepted: March 10, 2015
Corresponding author: Masahiro Goto, Division of Endocrinology and Metabolism, Tokyo Metropolitan Children's Medical Center, 2-8-29 Musashidai, Fuchu, Tokyo 183-8561, Japan
E-mail: masahiro_gotou@tmhp.jp

However, we have already reported that this regimen featuring administration of prednisolone for approximately 20 d can cause adrenocortical suppression in a high proportion of treated children, which is restored within 6 mo (3). There was also a significant correlation between morning serum cortisol values 1 wk after the cessation of prednisolone treatment and peak serum cortisol values at the following CRH stimulation test. On the basis of these results, we suggested that the residual adrenocortical function following the cessation of initial prednisolone treatment might be estimated with the single serum cortisol value at 09:00 h (3).

This study had two objectives. The first was to establish the cutoff point for the morning serum cortisol value as a threshold of intact adrenocortical function by using previously reported data in children (3). The second was to assess the efficacy of the morning cutoff point as determined above in estimating the adrenocortical function of newly recruited children with KD.

## Subjects and Methods

A prospective study of patients from one medical institution was performed. The subjects were 72 newly diagnosed children with KD with risk scores for IVIG unresponsiveness (1) of five points or higher who were administered a combination treatment of IVIG plus prednisolone (2) from February 2012 to March 2014. Fourteen children were excluded in advance because of episodes of unresponsiveness and extra steroid pulse therapy, 4 children were excluded in advance because of episodes of recurrence and extra steroid administration, and 6 children were excluded in advance because of a history of previous administration of steroids at their primary hospitals. The 72 children were divided into 2 subgroups according to the date of the initial prednisolone treatment for KD, namely, group A (already reported) (3) (treated between February and June 2012; n = 21) and group B (treated between July 2012 and March 2014; n = 51).

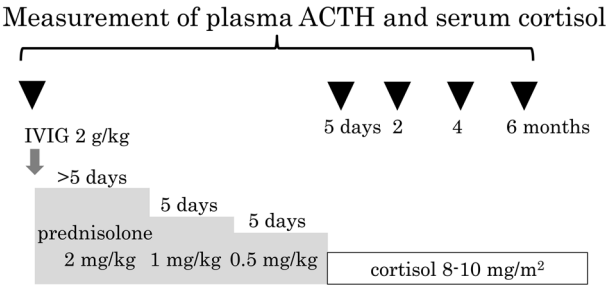


**Fig. 1.** Protocol of the study in group B. Closed triangles show the days when blood samples were collected.

As previously reported, cortisol coverage was started at a physiological dose of 8–10 mg/m$^2$/day in three divided doses after the cessation of prednisolone treatment in group A (3). The dose was increased to 80–100 mg/m$^2$/day in the event of stress such as febrile episodes. Blood samples were collected for measurement of serum cortisol and plasma ACTH at 09:00 h 4–8 d after the initiation of daily cortisol administration. CRH stimulation tests were performed within 12 d after the last collection of blood samples; and then repeated 2 and 6 mo afterwards in patients whose peak serum cortisol levels in the previous CRH stimulation tests were lower than 20 mcg/dL (3).

In group B, cortisol coverage was started after the cessation of prednisolone treatment in the same protocol as in group A. In this group, blood samples were collected to measure serum cortisol and plasma ACTH values at random times on the day of admission, at 09:00 h approximately 5 d after the cessation of prednisolone treatment (0 mo); and at 2, 4; and 6 mo afterwards until coverage was completed (Fig. 1). Daily administration of physiologic cortisol was stopped when the measured serum cortisol value exceeded 2.5 mcg/dL. The administration of high-dose cortisol during episodes of stress was also stopped when the serum cortisol value exceeded 5 mcg/dL. The CRH stimulation test was

subsequently performed to confirm the recovery of adrenocortical function. A peak serum cortisol level of more than 15 mcg/dL was considered as an index of full adrenocortical recovery.

Clinical episodes of adrenal insufficiency were checked in both group A and group B by viewing medical charts.

All statistical analyses were conducted with SPSS Statistics 20 (IBM). Continuous variable data are expressed as the range with the median. A nonparametric Mann-Whitney test was used to compare these data between group A and group B. Fisher's exact test was used to compare the ratio of each sex between these groups. Using the data of group A at 0, 2, and 6 mo after the cessation of prednisolone treatment, receiver operating characteristic (ROC) curves were constructed to determine the optimal cutoff value for morning serum cortisol levels indicating full adrenocortical recovery (peak serum cortisol values > 15 mcg/dL). Kaplan-Meier curves were constructed to calculate the ratios of cumulative patients whose serum cortisol values exceeded either 2.5 mcg/dL or 5 mcg/dL by 0, 2, 4; or 6 mo after the cessation of initial prednisolone treatment. Another Kaplan-Meier curve indicating the ratio of cumulative patients with either a single serum cortisol value of > 5 mcg/dL or a peak serum cortisol value of > 15 mcg/dL in the CRH stimulation test was also constructed. A $p$ value of less than 0.05 was taken as an indicator of a significant difference.

This study was conducted in accordance with the ethical principles set out in the Declaration of Helsinki; and with the ethical guidelines for epidemiological studies issued by the Ministry of Health, Labour and Welfare in Japan. The study was approved by the ethics review board of Tokyo Metropolitan Children's Medical Center (ID: H23-75). Informed consent was obtained from the parents at enrollment.

## Results

The background characteristics of the patients are shown in Table 1. There was no significant difference in age at the initiation of treatment, ratio of each sex, risk score for coronary artery complications, duration of prednisolone treatment; and cumulative dose of steroids between groups A and B (Table 1).

ROC curves for the morning serum cortisol levels in group A are shown in Fig. 2. The areas under the ROC curve ($AUC_{ROC}$) were 0.888 at 0 mo (Fig. 2A) and 0.732 in the combined data for 2 and 6 mo (Fig. 2B). Thresholds of 4.95 mcg/dL at 0 mo and 5.95 mcg/dL in the combined data for 2 and 6 mo after the initial prednisolone treatment maximized the sum of the sensitivity (0.800 and 0.640, respectively) and specificity (0.875 and 0.800, respectively) of adrenocortical recovery confirmed by the peak serum cortisol levels (> 15 mcg/dL) (Fig. 2). On the basis of these results, we established a serum cortisol value at 09:00 h of 5 mcg/dL as the threshold for an index of intact adrenocortical function. The sensitivity of this cutoff value was 0.800 at 0 mo and 0.760 in the combined data for 2 and 6 mo after the initial prednisolone treatment. The specificity values were 0.875 and 0.6, respectively. We also arbitrarily defined half the value (2.5 mcg/dL) of the abovementioned threshold as an index of partial recovery of adrenocortical function and for stopping daily physiologic cortisol coverage.

In group B, the serum cortisol value at 09:00 h approximately five days after the cessation of prednisolone was suppressed to below 5 mcg/dL in 38 out of 51 patients (74.5%) and to below 2.5 mcg/dL in 26 patients (51.0%) (Fig. 3B). Serum cortisol values at 09:00 h were restored to above 2.5 mcg/dL in all of the patients by 2 mo after the cessation of initial prednisolone treatment, and daily physiologic cortisol coverage could be stopped by this time (Fig. 4A). Among 50 patients who could be followed up until 6 mo after the cessation of initial prednisolone treatment, it was confirmed in 46 (92%) that the morning serum cortisol values were restored to above 5 mcg/dL by this time (Fig. 4B). The peak serum cortisol values in the CRH stimulation tests performed

**Table 1** Background characteristics of the patients

| | Group A | Group B | *p* value |
|---|---|---|---|
| Age (yr) | 0.3–10.4 (median 3.1) | 0.3–10.0 (median 3.3) | 0.552 |
| Sex (M/F) | 13/8 | 24/27 | 0.305 |
| Risk scores | 5–9 (median 7) | 5–10 (median 6) | 0.385 |
| Duration of prednisolone treatment (d) | 16–26 (median 22) | 14–31 (median 22) | 0.826 |
| Cumulative doses of steroids (mg/m$^2$)* | 1626–3688 (median 2656) | 1400–3913 (median 2789) | 0.179 |

*Calculated as cortisol equivalence.

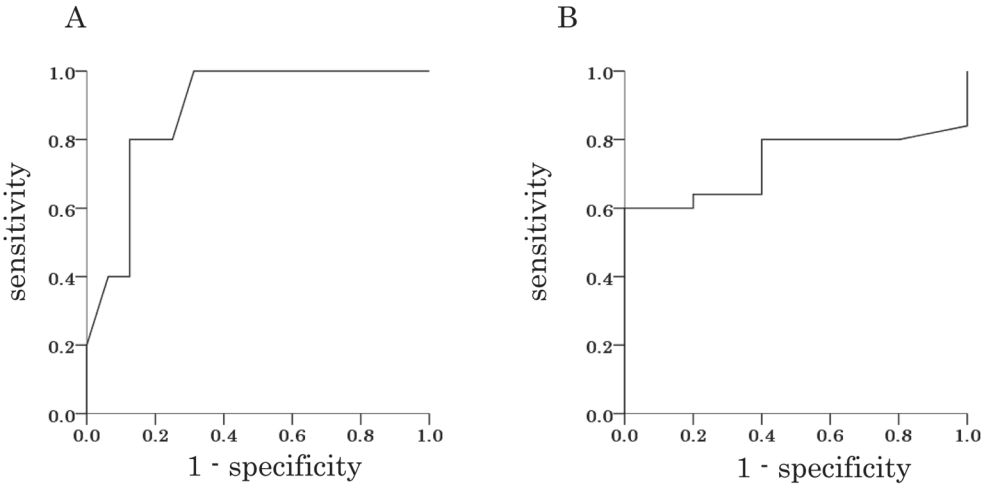


**Fig. 2.** ROC curves of morning serum cortisol levels in group A. (A) At 0 mo, (B) Combined data of 2 and 6 mo.

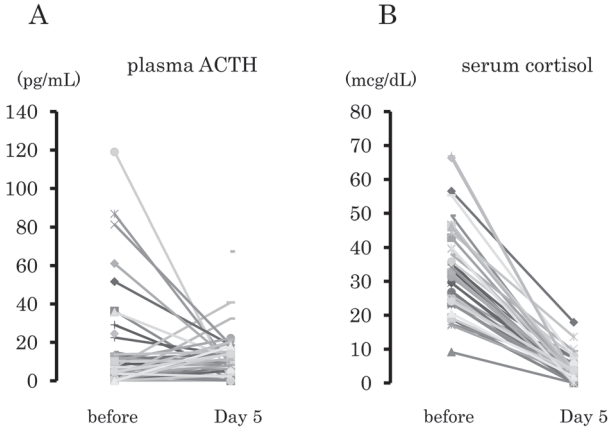


**Fig. 3.** Changes in morning plasma ACTH (A) and serum cortisol (B) values between before and 5 d after the prednisolone treatment in group B.

for 28 patients after observation of morning serum cortisol values > 5 mcg/dL ranged from 11.9 to 27.6 mcg/dL (median 17.9 mcg/dL). The peak serum cortisol values exceeded 15 mcg/dL in 25 of them (89.3%) (Fig. 5A). Forty-nine out of the 50 patients were confirmed to show either single serum cortisol values > 5 mcg/dL or peak serum cortisol values > 15 mcg/dL by 6 mo after the initial prednisolone treatment (Fig. 5B).

None of the patients in groups A and B were complicated with overt adrenal insufficiency during the study period, although the possibility that patients with minor adrenal insufficiency had been overlooked because of their failure to consult for their symptoms cannot be ruled out.

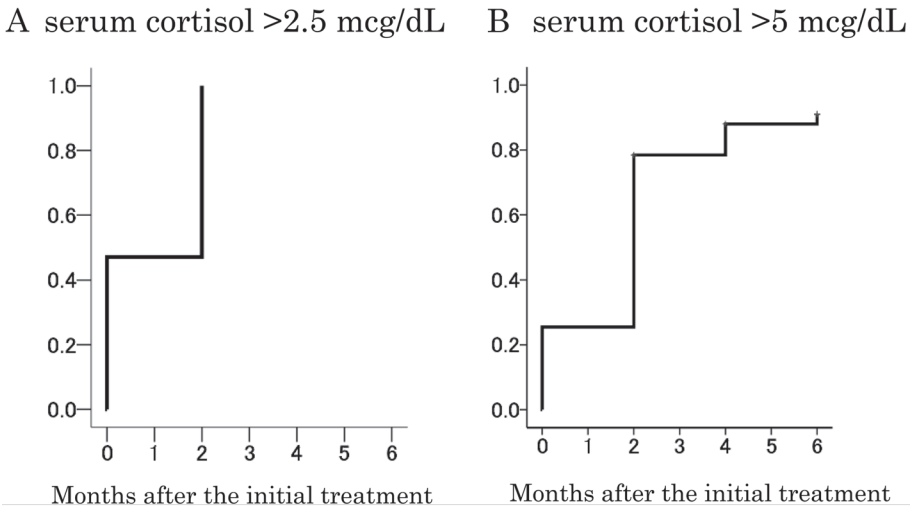


**Fig. 4.** Kaplan-Meier curves indicating the cumulative ratios of patients whose serum cortisol values at 09:00 h exceeded either 2.5 mcg/dL (A) or 5 mcg/dL (B) in group B.

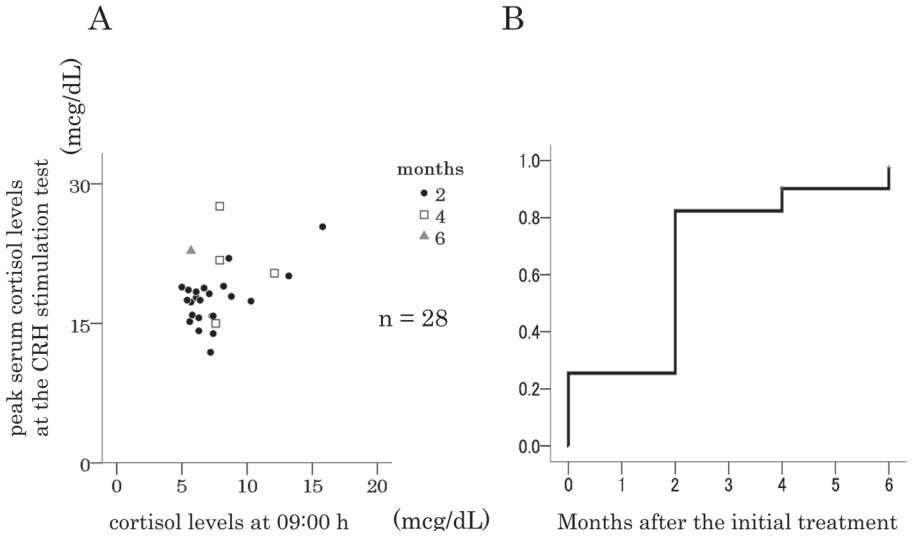


**Fig. 5.** (A) Peak serum cortisol values at the CRH stimulation test in relation to serum cortisol values at 09:00 h in 28 patients whose morning serum cortisol values at 2, 4, or 6 mo exceeded 5 mcg/dL in group B. (B) Kaplan-Meier curve indicating the cumulative ratio of patients with either a serum cortisol value at 09:00 h > 5 mcg/dL or peak serum cortisol value > 15 mcg/dL in the CRH stimulation test in group B.

## Discussion

In this study, we established a serum cortisol value at 09:00 h of 5 mcg/dL as an index of intact adrenocortical function using ROC curves constructed with the data of 21 previously reported patients: group A in this manuscript (3). Subsequently, we examined serum cortisol values at 09:00 h in 51 newly recruited patients to confirm that single serum cortisol values at 09:00

h can be indices of adrenocortical recovery even 2 to 6 mo after cessation of the initial prednisolone treatment. Approximately 90% of the patients with morning serum cortisol values above 5 mcg/dL 2 to 6 mo after cessation of the initial prednisolone treatment had peak serum cortisol values exceeding 15 mcg/dL, suggesting the efficacy of this approach. Adrenocortical function could be restored within 6 mo in most of them.

Care must be taken to avoid adrenal insufficiency in children with KD treated with prednisolone. As we have mentioned above and previously reported (3), adrenocortical suppression can be observed in a high proportion of children treated with this regimen. As recurrent fever is not unusual in children with KD due to exacerbation or recurrence of the disease, it is advisable to ensure sufficient cortisol coverage to avoid adrenal insufficiency when the existence of adrenocortical suppression is revealed. Therefore, we emphasize the importance of the strategy of evaluating a single morning serum cortisol value for screening of the residual adrenocortical function in these children with KD.

The main strength of this study is the accumulation of data supporting the validity of applying single cortisol values at 09:00 h for the estimation of adrenocortical recovery in our KD patients. This finding is inconsistent with a previous report suggesting that serum cortisol responses to the CRH stimulation test could not be predicted by measuring the basal serum cortisol value (4). However, this discrepancy may be explained by the subjects' heterogeneity in terms of their backgrounds, such as their primary disease, and the dose and duration of the administered steroids. The differences in age and ethnicity between their subjects and ours might be another explanation. Single blood sample collection for evaluation of the morning serum cortisol value at 09:00 h can be easily performed in any medical facility during normal opening hours.

There are several limitations in terms of interpreting our results. First, although we chose to check the residual adrenocortical function in our patients every two months, its recovery might have been confirmed earlier and redundant cortisol coverage could have been stopped earlier if we had repeated the examination every month.

Second, we cannot rule out the possibility that the cortisol coverage applied to these patients itself may have delayed full recovery of their adrenocortical function. Indeed, the adrenocortical function of children with acute lymphoblastic leukemia treated with either prednisolone or dexamethasone was reported to recover earlier without cortisol coverage than in our patients, despite longer durations of administration and higher administered doses of glucocorticoid than in our patients (5, 6). However, in all of the newly diagnosed patients in group B, daily administration of physiologic cortisol could be stopped within two months, and the total sum of administered cortisol was approximately one-fifth of the preceding prednisolone administration, at most.

Third, the rationality of defining a peak serum cortisol value in the CRH stimulation test > 15 mcg/dL as indicating intact adrenal function in this study leaves room for discussion. We applied a peak serum cortisol value > 20 mcg/dL in our previous study (3) as an index of full adrenocortical recovery following the definition of Schlaghecke *et al.* (4). On the other hand, Tanaka *et al.* defined the normal range of peak cortisol values for the test in children as 13.1–35.6 mcg/dL (7). We arbitrarily settled on 15 mcg/dL as the cutoff value based on our experience that a considerable portion of children with idiopathic short stature had peak serum cortisol values between 15 mcg/dL and 20 mcg/dL (data not shown).

In summary, single sampling of the serum cortisol value at 09:00 h is a useful tool to estimate the residual adrenocortical function in KD patients treated with the combination of IVIG plus prednisolone. A serum cortisol value of higher than 5 mcg/dL at this time can be a practical index of intact adrenocortical function.

## Acknowledgments

We would like to thank all of the staff at the Division of Endocrinology and the Department of General Pediatrics in our hospital for their contribution to the initial treatment of KD and subsequent examinations.

## References

1. Kobayashi T, Inoue Y, Takeuchi K, Okada Y, Tamura K, Tomomasa T, *et al*. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. Circulation 2006;113: 2606–12. [Medline] [CrossRef]
2. Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, *et al*. RAISE study group investigators Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. Lancet 2012;379: 1613–20. [Medline] [CrossRef]
3. Goto M, Miyagawa N, Kikunaga K, Miura M, Hasegawa Y. High incidence of adrenal suppression in children with Kawasaki disease treated with intravenous immunoglobulin plus prednisolone. Endocr J 2015;62: 145–51. [Medline] [CrossRef]
4. Schlaghecke R, Kornely E, Santen RT, Ridderskamp P. The effect of long-term glucocorticoid therapy on pituitary-adrenal responses to exogenous corticotropin-releasing hormone. N Engl J Med 1992;326: 226–30. [Medline] [CrossRef]
5. Cunha CF, Silva IN, Finch FL. Early adrenocortical recovery after glucocorticoid therapy in children with leukemia. J Clin Endocrinol Metab 2004;89: 2797–802. [Medline] [CrossRef]
6. Rix M, Birkebaek NH, Rosthøj S, Clausen N. Clinical impact of corticosteroid-induced adrenal suppression during treatment for acute lymphoblastic leukemia in children: a prospective observational study using the low-dose adrenocorticotropin test. J Pediatr 2005;147: 645–50. [Medline] [CrossRef]
7. Tanaka T, Hibi I, Shimizu N, Imura H, Tanaka K, Fukata J, *et al*. Evaluation of hypothalamo-pituitary-adrenocortical function in children by human corticotropin-releasing hormone (MCI-028) test. Endocr J 1993;40: 581–9. [Medline] [CrossRef]