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Original Article

Efficacy of single serum cortisol reading obtained between 9 AM and 10 AM as an index of adrenal function in children treated with glucocorticoids or synthetic adrenocorticotropic hormone

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Abstract. To find a simple method to screen for iatrogenic childhood adrenal insufficiency, we retrospectively examined the results of CRH stimulation tests performed 212 times on 111 subjects (68 males; age at commencement of initial treatment ranged 0.0–19.8 yr; median age, 5.8 yr). Before the commencement of this study, 97 subjects had been treated with glucocorticoids and 14 subjects with West syndrome had been treated with synthetic adrenocorticotropic hormone. Duration of the primary treatment ranged from 15 to 2150 days. CRH stimulation tests were conducted between 09:00 AM and 10:00 AM and peak cortisol values less than 15 μg/dL were considered indicative of adrenal insufficiency. The receiver operating characteristic curve showed that the optimal basal serum cortisol cut-off values when screening for adrenal suppression ranged from 5.35 to 5.80 μg/dL depending on the primary disease. All subjects having a serum cortisol value of less than 2.3 μg/dL had insufficient adrenal function while all subjects having greater than 11 μg/dL had intact adrenal function. We concluded that single serum cortisol values obtained between 09:00 AM and 10:00 AM had the potential to serve as an index of adrenal function in children treated with glucocorticoids or synthetic adrenocorticotropic hormone.

Key words: adrenal suppression, single serum cortisol, glucocorticoids, synthetic adrenocorticotropic hormone

Introduction

Iatrogenic adrenal insufficiency is one of the major causes of adrenal failure in the pediatric population (1). Glucocorticoids, used primarily to treat various diseases such as autoimmune diseases (2) and neoplastic disorders (3), can cause iatrogenic adrenal insufficiency by suppressing the hypothalamus-pituitary-adrenal axis after prolonged use (1–3). There has been no report of adrenal suppression caused by synthetic adrenocorticotropic hormone therapy among infants with West syndrome. However,

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Table 1 Background characteristics of subjects

	Population	IBD	Purpura	West syndrome	Others
Sex (M/F)	68/ 43	28/12	13/7	8/6	19/18
Age at start of initial treatment (yrs)	0.0–19.8 (median 5.8)	3–15.7* (median 11.7)	2–7.5* (median 5)	0.3–1.5 (median 0.6)	0.0–19.8 (median 3.05)
Duration of initial treatment (d)	15–2150 (median 47)	21–300* (median 64.5)	15–220 (median 27)	26–36 (median 29)	17–2150 (median 66.5)
Number of CRH stimulation tests	212	85	50	16	61

IBD: inflammatory bowel disease. * Statistically significant difference compared with West syndrome group.

frequent use of this synthetic drug and the resultant protracted secretion of cortisol from the adrenal glands may cause suppression of the hypothalamus-pituitary-adrenal axis. Adrenal failure can be fatal if untreated (1, 4–6), and must therefore be diagnosed and treated immediately.

A simple method of screening pediatric patients for iatrogenic adrenal insufficiency is crucial for clinical practice for two reasons. First, many pediatric patients receive glucocorticoids or synthetic adrenocorticotropic hormone as part of their treatment. Second, some pediatric patients require repeated assessment of adrenal function. However, repetitive stimulation tests for adrenal function can be stressful. Previously, we reported that single serum cortisol values obtained at 09:00 AM correlated significantly with peak cortisol values in a CRH stimulation test in children with Kawasaki disease treated with prednisolone for approximately 20 days (7). We also reported that a single cortisol value higher than 5 μg/dL obtained at 09:00 AM can be a practical index of intact adrenal function in these children (8).

Here we report that a single cortisol value obtained between 09:00 AM and 10:00 AM could serve as a tool to screen for adrenal suppression in children treated with glucocorticoids for a primary disease other than Kawasaki disease, and in children treated with synthetic adrenocorticotropic hormone for West syndrome.

Subjects and Methods

Patients

The patients used received treatment at a single medical institution. Between March 2010 and October 2014, the CRH stimulation test was performed 220 times on 116 children, who had previously been treated either with glucocorticoids for a primary disease other than Kawasaki disease or with a synthetic adrenocorticotropic hormone for West syndrome. Eight tests performed on children younger than 6 mo were excluded due to uncertainty regarding the establishment of circadian rhythm at this age (9). The remaining 212 tests, performed on 111 children (68 boys and 43 girls), were included in the following study (Table 1). The primary diseases of subjects were categorized as inflammatory bowel diseases (IBD), including ulcerative colitis and Crohn's disease (n = 40), a subgroup including Henoch-Schonlein purpura and idiopathic thrombocytopenic purpura (referred as purpura hereafter) (n = 20), West syndrome (n = 14), and others (n = 37) including diseases such as leukemia and biliary atresia. There was no significant difference in the gender ratio between groups.

The age at commencement of glucocorticoid or synthetic adrenocorticotropic hormone therapy ranged from 0.0 to 19.8 yr (median 5.8 yr) for the total subject population (hereafter,

'population'). Among subjects with IBD, purpura, West syndrome, and others, the age range was 3 to 15.7 yr (median 11.7 yr), 2 to 7.5 yr (median 5 yr), 0.3 to 1.5 yr (median 0.6 yr), and 0.0 to 19.8 yr (median 3.05 yr), respectively. The age at initial treatment was significantly lower in children with West syndrome treated with synthetic adrenocorticotropic hormone than in the IBD or purpura groups. The duration of treatment ranged from 15 to 2150 days for the population (median 47 days). Specifically, the treatment duration ranged from 21 to 300 d (median 64.5 d) for IBD patients, 15 to 220 d (median 27 d) for purpura patients, 26 to 36 d (median 29 d) for West syndrome patients, and 17 to 2150 d (median 66.5 d) for subjects with other primary diseases. The duration of the initial treatment was significantly longer for children with IBD than for those with West syndrome.

Methods

A retrospective chart review was conducted and the data from CRH stimulation tests were analyzed. Patients initially treated with glucocorticoids were prescribed oral cortisol at a physiological dose (8–10 mg/m^2/d) daily and at a dose of 80–100 mg/m^2/d in the event of stress such as febrile episodes. The patients with West syndrome, initially treated with synthetic adrenocorticotropic hormone, had not been administered oral cortisol. The test commenced between 09:00 AM and 10:00 AM after overnight fasting. The patients were requested not to take any glucocorticoids on the day of the examination. A dose of 1.5 μg/kg (max. dose 100 μg) of human CRH (Tanabe; Tanabe Mitsubishi Corporation, Osaka, Japan) was administered intravenously and blood samples were drawn at 0, 15, 30, 60, 90, and 120 min after treatment to measure serum cortisol and ACTH concentrations. The details of the kits used for this purpose and their precision are discussed elsewhere (7).

Based on peak cortisol values from the CRH stimulation test, all subjects as well as those in primary disease groups (IBD, purpura, West syndrome, and others) were further divided into two subgroups. One group had insufficient adrenal function (peak cortisol values < 15 μg/dL) and the other with intact adrenal function (peak cortisol values > 15 μg/dL), in accordance with the definition applied in our previous study (8). Scatter diagrams were then constructed, and the overlap of the two subgroups was calculated. Receiver operating characteristic (ROC) curves were also produced to calculate the optimal cut-off values (the points where the sum of sensitivity and specificity becomes maximum) for pre-test serum cortisol levels, to predict intact adrenal function (peak cortisol values > 15 μg/dL). These were also used to calculate the area under the curve (AUC) and *p* values for both the whole population and the four primary disease groups. Based on the results of these analyses, the sensitivity, specificity, and likelihood ratio were calculated with pre-test serum cortisol cut-off values posited at 5 μg/dL and 5.5 μg/dL.

Oral informed consent was obtained from the guardians before the stimulation tests. Data from previously performed stimulation tests were presented on the condition that the privacy of the subjects would be protected according to requirements of the ethics review board of Tokyo Metropolitan Children's Medical Center (ID: H27b-126).

Statistical analysis

All statistical analyses and construction of graphics (scatter diagrams and ROC curves) were done using SPSS Statistics 20 (IBM). Continuous variable data were expressed as a range with a median. A nonparametric Mann-Whitney test was used to compare the data of the primary disease groups. A Fisher's exact test was used to compare the gender ratios among these groups.

Results

The distribution of pre-test serum cortisol values is shown in Fig. 1. The whole population and the four primary disease groups were further

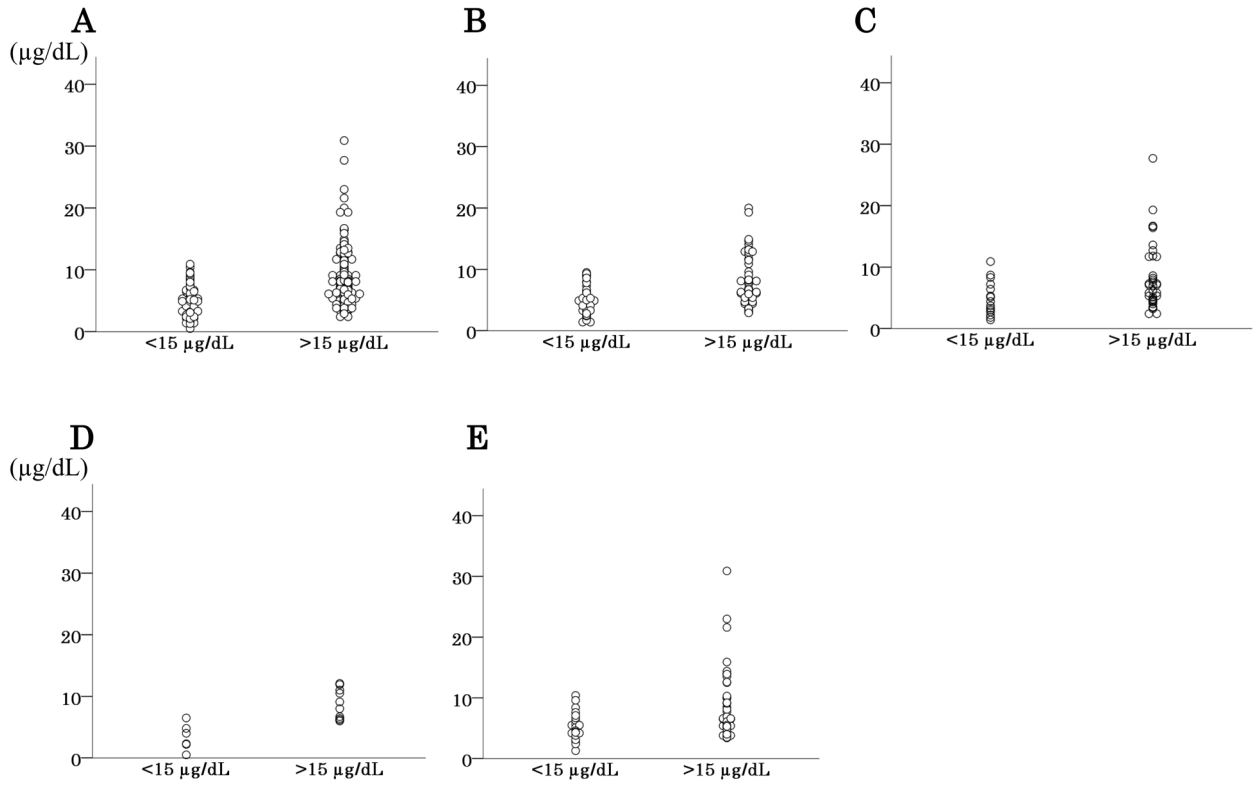

Fig. 1. Distribution of the pre-test serum cortisol values in the population (A), and IBD (B), purpura (C), West syndrome (D), and others (E) groups. Subjects were divided into subgroups based on insufficient adrenal function (peak cortisol values < 15 μg/dL) or intact adrenal function (peak cortisol values > 15 μg/dL).

divided into two subgroups as mentioned above. The overlap of pre-test serum cortisol values among the West syndrome group (Fig. 1D), both for subjects with insufficient adrenal function and for those with intact adrenal function, was observed in 25% of the population. However, the overlap of cortisol values in these subgroups among the population (Fig. 1A), IBD (Fig. 1B), purpura (Fig. 1C), and other groups (Fig. 1E) was observed to be 77%, 72%, 74%, and 74% of their members, respectively. Within the population, all subjects with a serum cortisol value less than 2.3 μg/dL at 0 min showed insufficient adrenal function, whereas all subjects with a value greater than 11 μg/dL showed intact adrenal function.

The ROC curves for pre-test serum cortisol values are shown in Fig. 2. For the population, the threshold maximizing the sum of sensitivity and specificity of intact adrenal function, AUC_{ROC}, and p value were 5.35 μg/dL, 0.756, and 0.000, respectively (Fig. 2A). The threshold, AUC_{ROC}, and p values were 5.35 μg/dL, 0.759, and 0.000 for the IBD group (Fig. 2B), 5.55 μg/dL, 0.713, and 0.018 for the purpura group (Fig. 2C), 5.40 μg/dL, 0.950, and 0.003 for the West syndrome group (Fig. 2D), and 5.80 μg/dL, 0.736, and 0.002 for the others group (Fig. 2E), respectively.

Table 2 shows the degrees of sensitivity, specificity, and the likelihood ratio when the pre-test serum cortisol cut-off values were posited at 5 μg/dL and 5.5 μg/dL. The sensitivity was 1.000, the specificity was 0.833, and the likelihood ratio was 6 at both cut-off values for subjects with West syndrome. In contrast, those figures were lower in the population, IBD, purpura, and others groups.

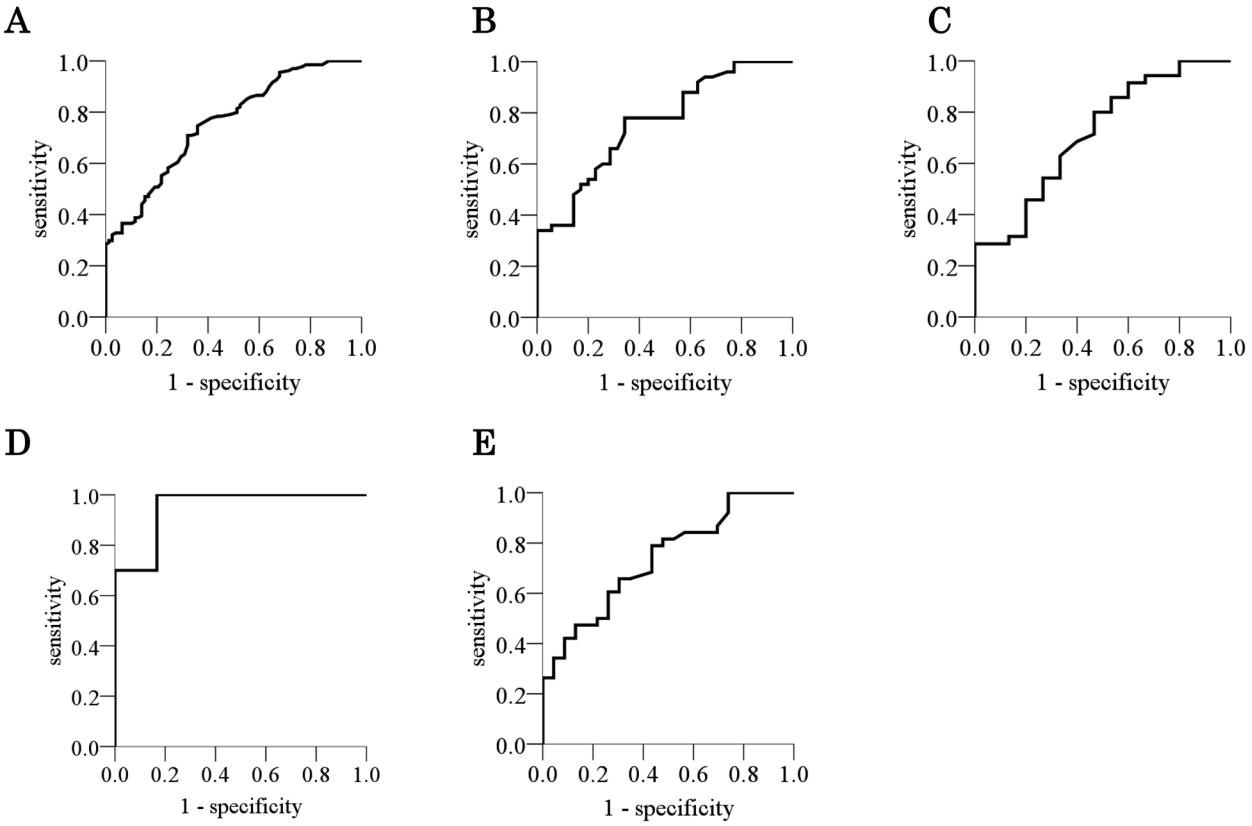

Fig. 2. ROC curves of the pre-test serum cortisol values in the population (A), and IBD (B), purpura (C), West syndrome (D), and others (E) groups.

Table 2 Diagnostic accuracy of cutoff values for morning serum cortisol levels among patients with different diseases

	Population	IBD	Purpura	West syndrome	Others
Sensitivity	0.784	0.780	0.714	1.000	0.789
	0.716	0.780	0.629	1.000	0.684
Specificity	0.564	0.543	0.533	0.833	0.522
	0.641	0.657	0.666	0.833	0.565
Likelihood ratio	1.8	1.7	1.5	6	1.7
	2.0	2.3	1.9	6	1.6

Upper row: cutoff value for serum cortisol levels = 5.0 μg/dL. Lower row: cutoff value for serum cortisol levels = 5.5 μg/dL. IBD: inflammatory bowel disease.

Discussion

This study demonstrated that optimal cut-off values of serum cortisol, obtained from sampling between 09:00 AM and 10:00 AM for screening for adrenal suppression in children treated with either glucocorticoids or synthetic adrenocorticotropic hormone, ranged from 5.35 to 5.80 μg/dL depending on the primary disease. In addition, all subjects with serum cortisol values less than 2.3 μg/dL, during this time frame, showed insufficient adrenal function, whereas

all subjects with values greater than 11 μg/dL showed intact adrenal function.

Current emphasis on adrenal insufficiency as a potentially fatal disorder has led to the recognition of the importance of rapid diagnosis and treatment (1, 4–6). Several proposals for managing adrenal insufficiency have already been published (10–13). Moreover, the guidelines recently published by the Japan Endocrine Society state that adrenocortical insufficiency can be excluded in patients with morning (by 09:00 AM) serum cortisol values greater than 18 μg/dL, but should be highly suspected in those with values of less than 4 μg/dL (14), for the same period. However, it should be noted that these figures were based on data obtained previously from an adult population (15, 16).

Our study, based on results of the CRH stimulation test performed in more than 100 children, has the following advantages. First, the study has demonstrated that single serum cortisol values obtained between 09:00 AM and 10:00 AM, a more practical time frame for routine clinical practice, can be applied to screening for adrenal suppression in children suspected of iatrogenic adrenal insufficiency. Previous reports and reviews recommended measuring serum cortisol values between 06:00 AM and 08:00 AM, and considered 10 μg/dL as an appropriate cut-off value for intact adrenal function (3, 17). Second, the study established specific values for serum cortisol levels based on data obtained from children with suspected iatrogenic adrenal insufficiency, which can accurately confirm either insufficient adrenal function or intact adrenal function. Third, the data presented in this report can more reliably be applied to children.

This study has the following limitations. First, as this was a retrospective study, blood samples were not collected at exactly the same time. The time of collection for each subject varied widely from 09:00 AM to 10:00 AM. Normally, later collection times correspond to lower serum cortisol levels. Thus, the variation in collection time may have influenced the results.

Second, the variation in the duration of glucocorticoid administration, which depended on the subjects' primary disease and clinical course, may have influenced our results. Most subjects with IBD, and some subjects with purpura or some other primary disease, were treated with glucocorticoids for a relatively long time. Some of these subjects showed peak serum cortisol values of less than 15 μg/dL in the CRH stimulation test even when serum cortisol values at 0 min exceeded 10 μg/dL (Fig. 1B, C, E). This may be one reason why the degrees of AUC in these categories were not as high as that in subjects with West syndrome or Kawasaki disease (8). We could not get satisfactorily high degrees of AUC from ROC curves even when we divided our subjects (excluding patients with West syndrome) into subgroups according to the duration of initial treatment (data not shown). This may be attributed to the diversity of their primary diseases and variable total doses during initial treatments. However, the optimal cut-off values showed a tendency to fall into the range of 5.35 to 5.80 μg/dL for all subjects regardless of differences in primary disease or duration of primary treatment. This finding suggests that serum cortisol values collected between 09:00 AM and 10:00 AM, as well as those collected conventionally between 06:00 AM and 08:00 AM, can also be applied to screen for adrenal suppression through a simple lowering of the cut-off values.

In conclusion, single serum cortisol values obtained between 09:00 AM and 10:00 AM can serve as a potential index of adrenal suppression in children suspected of iatrogenic adrenal insufficiency. Adrenal suppression can be either confirmed or excluded when serum cortisol values obtained are either less than 2.3 μg/dL or greater than 11 μg/dL.

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Conflict of Interest: None of the authors has any potential conflicts of interest associated with this research.

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