ORIGINAL

An attempt to create a treatment algorithm of central adrenal insufficiency using CRH test, DHEA-S and clinical evaluation

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Abstract : Objective : To examine diagnostic performance of corticotropin-releasing hormone (CRH) test combined with baseline dehydroepiandrosterone sulfate (DHEA-S) in patients with a suspect of central adrenal insufficiency. Methods : Patients (n=215) requiring daily or intermittent hydrocortisone replacement, or no replacement were retrospectively checked with their peak cortisol after CRH test and baseline DHEA-S. Results : None of 106 patients with the peak cortisol ≥ 17.5 μg/dL after CRH test required replacement, and all 64 patients with the peak cortisol < 10.0 μg/dL required daily replacement. Among 8 patients with 10.0 μg/dL ≤ the peak cortisol < 17.5 μg/dL and baseline DHEA-S below the reference range, 6 patients required daily replacement and 1 patient was under intermittent replacement. Among 37 patients with 10.0 μg/dL ≤ the peak cortisol < 17.5 μg/dL and baseline DHEA-S within the reference range, 10 and 6 patients were under intermittent and daily replacement, respectively. Conclusions : No patients with the peak cortisol ≥ 17.5 μg/dL required hydrocortisone replacement, and all patients with the peak cortisol below 10.0 μg/dL required daily replacement. Careful clinical evaluation was required to determine requirement for replacement in patients with 10.0 μg/dL ≤ the peak cortisol < 17.5 μg/dL even in combination with baseline DHEA-S. J. Med. Invest. 69 : 287-293, August, 2022

Keywords **:** *central adrenal insufficiency, corticotropin-releasing hormone (CRH) test, dehydroepiandrosterone-sulfate (DHEA-S), retrospective cohort study, treatment algorithm*

INTRODUCTION

Hypopituitarism causes hypogonadism, growth hormone deficiency, hypothyroidism, and adrenal insufficiency (1). Especially, central adrenal insufficiency is a critical condition which requires accurate assessment of its severity and rapid determination of the amount of replacement (2). Various tests have been used, and insulin tolerance test (ITT) has been regarded as the gold standard test for the diagnosis of central adrenal insufficiency (3). However, because ITT causes hypoglycemia which promotes cortisol secretion via stimulation of adrenocorticotropic hormone (ACTH), close supervision during the test is mandatory. In addition, because hypoglycemia aggravates ischemic heart diseases and may trigger seizures, ITT is contraindicated in patients with these disorders (2, 4). Overnight metyrapone test has also been used commonly, but there is a limitation in the reliability of 11-deoxycortisol assay and metyrapone is not in the market but has to be obtained directly from the manufacturer (Novartis, Basel, Switzerland) (5). Rapid ACTH test has the advantage of being simpler to perform than ITT or metyrapone test with almost no side effects (6), and can identify patients with profound or long-standing ACTH insufficiency. However, if ACTH insufficiency is moderate or developed recently, adrenocortical atrophy is incomplete and the ACTH stimulation can show a normal response, even though the patient is actually ACTH deficient (6). Corticotropin releasing hormone (CRH) test is also simple to perform, has very few side effects, and can be widely applied to patients. However, there has been a criticism that the test is not of much help in the actual diagnosis of the condition because of relatively low sensitivity and specificity (2, 5). One of the other problems about CRH test is that not large enough number of subjects were evaluated in determining the cut-off value of the test (4). Schmidt *et al*. compared the results of ITT with those of CRH test. They concluded that CRH test is not sensitive enough for the diagnosis of central adrenal insufficiency, but that the peak serum cortisol after CRH stimulation showed good correlation with that after ITT (7).

Because of the progress of aging society, there is a necessity for safely diagnosing central adrenal insufficiency in elderly patients who may suffer from coronary ischemia, arrhythmias and other cardiovascular diseases. Because CRH test does not cause hypoglycemia and has been well tolerated in most patients, CRH test may be the one to choose for the diagnosis of central adrenal insufficiency with safety in the elderly or patients with ischemic heart diseases. Thus, it is worthwhile to examine whether the results of CRH test can be used in place of ITT in evaluating central adrenal insufficiency.

The most important clinical demand for the diagnosis of central adrenal insufficiency is to distinguish patients with need for

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replacement therapy from those without need for replacement. It is also important to differentiate those patients who require constant daily replacement with absolute ACTH deficiency from those with relative ACTH deficiency requiring temporary replacement when the need for glucocorticoid exceeds its secretory capacity under stressful conditions. However, previous studies fell short of answering these clinical questions of whether a patient requires daily or intermittent hydrocortisone replacement.

In order to address these issues, 215 patients with a suspect of central adrenal insufficiency who underwent CRH test with baseline dehydroepiandrosterone sulfate (DHEA-S) measurement were followed for at least 2 years, and were determined for their requirement of daily or intermittent hydrocortisone replacement. By checking their peak cortisol after CRH test and baseline DHEA-S levels retrospectively, we have developed three-step algorithm for determining need for hydrocortisone replacement.

PATIENTS AND METHODS

This is a retrospective cohort study involving 223 patients who underwent CRH test between April 2011 and December 2018 in Tokushima University Hospital and its affiliated hospitals ; Tokushima Red Cross Hospital, Tokushima Prefecture Naruto Hospital, Tokushima Prefectural Central Hospital. We excluded 8 patients with missing or incomplete data, and analysis was performed in the remaining 215 patients.

CRH test was performed from 9 am to 11 am with overnight fasting and just after more than 30 minutes of bed rest, using 100 μg human CRH (Tanabe Mitsubishi, Tokyo, Japan). Blood samples were taken at baseline, 30, 60, 90 and 120 min for the measurement of serum cortisol. If patients were already under hydrocortisone replacement, hydrocortisone was stopped 18 hours before CRH test. Serum cortisol was measured using an electrochemiluminescence immunoassay (ECLIA) (Elecsys 2010 ; Roche Diagnostics, Mannheim, Germany).

All patients were originally diagnosed as normal adrenocortical function, or central adrenocortical insufficiency based upon the diagnostic criteria for CRH test in Japan (8). And then, patients were followed for at least 2 years to the maximum of 9 years (average 4.4 years). During those follow-up period, requirement of hydrocortisone replacement was adjusted by specialist of endocrinology with carefully assessment of patient's symptoms/signs and/or laboratory data of hydrocortisone under- or over-replacement and the final disposal of patients are shown in Fig 1. The basal and stimulated cortisol data after CRH test were evaluated for each final disposal of patients.

Data are expressed as means ± SD. Serum cortisol in each group was compared with Mann-Whitney U test between two groups, and multivariate analysis was performed using statistical software JMP 14.2 for Macintosh (SAS Institute Inc., Tokyo, Japan). ROC analysis was also performed with JMP 14.2 for Macintosh to find out the best cut-off points for distinguishing patients without replacement, and with intermittent or daily replacement. A p value of less than 0.05 was considered to be statistically significant. We calculated the specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV), and diagnostic accuracy of cut-off values for the peak cortisol after CRH administration. Diagnostic accuracy is calculated by the following formula (9) : true positive + true negative/total number x 100.

Serum DHEA-S was measured in most of the patients using baseline blood samples of CRH test. Serum DHEA-S was measured using chemiluminescent enzyme immunoassay (CLEIA) (SRL Inc, Tokyo, Japan). Reference range of each decade in males and females in Japan is taken from those by SRL, Inc (Tokyo, Japan).

https://test-guide.srl.info/hachioji/test/detail/004170602

	Male (μg/dL)	Female (μg/dL)
Age 18 to 20	24 - 537	51 - 321
Age 21 to 30	85 - 690	18 - 391
Age 31 to 40	106 - 464	23 - 266
Age 41 to 50	70 - 495	19 - 231
Age 51 to 60	38 - 313	8 - 188
Age 61 to 70	24 - 244	12 - 133
Age 71 and older	5 - 253	7 - 177

Because this study was planned after more than 2 years have passed since each patient underwent CRH test and baseline DHEA-S measurement, we informed all the outpatients at any of the affiliated hospitals, and oral consent was documented in the medical record. For those patients who were lost to follow, we posted a notice in the information board of each hospital that data from CRH test and baseline DHEA-S obtained from April, 2011 to November, 2018 be used anonymously for our study. For those patients who did not want to give consent to this study, we eliminated from the study. This study was approved by the Institutional Review Board of Tokushima University Hospital (No. 3393).

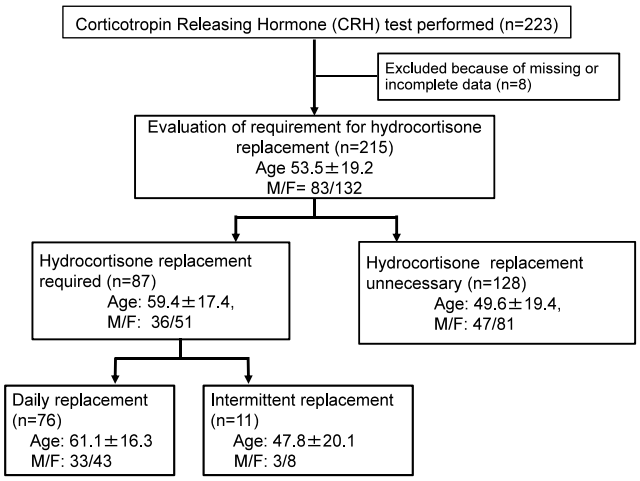

Figure 1. Flow diagram of entry subjects and results of CRH test. M ; male, F ; female

RESULTS

Among 223 patients who underwent CRH test, we eliminated 8 patients from the analysis because of missing or incomplete data. The final outcomes of 215 patients who were evaluated for requirement of hydrocortisone replacement are shown in Fig 1. There were 128 patients (47 males, 81 females, mean age 49.6) who did not require hydrocortisone replacement, and 87 patients (36 males, 51 females, mean age 59.4) who required hydrocortisone replacement. Among them, 76 patients (33 males, 43 females, mean age 61.1) were under daily replacement, and 11 patients (3 males, 8 females, mean age 47.8) were under intermittent replacement. Baseline characteristics and major complication just before CRH test are shown in Table 1 and causes of central adrenal insufficiency in these patients who need hydrocortisone replacement are shown in Table 2.

Adrenocortical insufficiency should be evaluated at both basal and stimulated conditions (10). Because serum cortisol levels at baseline, 30 minutes and the peak after CRH stimulation

Table 1. Baseline characteristics of the patients

Characteristic	Hydrocortisone replacement		*p* value
	Required (n = 87)	unnecessary (n = 128)	
Age (years)	59.4 ± 17.4	49.6 ± 19.4	< 0.001
Males/females	36/51	47/81	0.491
Body mass index (kg/m²)	24.2 ± 4.9	25.1 ± 20.8	0.742
Complications ; patient's number (%)			
Hypertension	24(28%)	31(24%)	0.579
Diabetes	17(20%)	24(19%)	0.884
Dyslipidemia	30(34%)	35(27%)	0.263
Obesity	23(26%)	32(25%)	0.821

Table 2. Causes of central adrenal insufficiency

Diagnosis	Number of patients	
1. Pituitary dysfunction	69	
Isolated ACTH deficiency		32
After surgical removal of pituitary tumors		29
Hypophysitis		4
Hemorrhage (e.g. Sheehan's syndrome)		3
Empty sella syndrome		1
2. Hypothalamic dysfunction	16	
Lymphatic infundibulo-hypophysitis		11
Chronic glucocorticoid treatment		5
3. Unknown cause	2	

showed better AUC than other time points in ROC analysis (7), serum cortisol levels at baseline, 30 minutes, and the peak after CRH stimulation were analyzed in each group of patients with or without hydrocortisone replacement (Fig 2). In most subjects, serum cortisol reached the peak at 60 to 90 minutes after CRH stimulation. Serum cortisol levels at 30 minutes and the peak after CRH stimulation were significantly lower in the intermittent replacement group compared to the group without replacement. Serum cortisol levels in the daily replacement group were significantly lower compared with those in the intermittent replacement and without replacement groups at all three time points (Fig 2). In order to find out which time point can separate these three groups best, ROC analysis was performed. ROC analysis of the peak value of serum cortisol after CRH stimulation revealed that area under the ROC (AUROC) was 0.990, and that the cut-off value for the diagnosis of adrenal insufficiency was 14.3 μg/dL with 95.3 % specificity and 93.1 % sensitivity (Fig 3C). In contrast, AUROC for serum cortisol levels at baseline and 30 minutes after CRH stimulation was 0.911 and 0.980, respectively, both of which were smaller than that at the peak after CRH stimulation (Fig 3A, 3B). Because we do not want to misdiagnose patients who require hydrocortisone replacement, it is better to adopt a cut-off value of the peak cortisol with highest sensitivity at or above 17.1 μg/dL for the diagnosis of adrenal insufficiency. Therefore, we propose cut-off value of the peak cortisol level of 17.5 μg/dL, which showed good performance with 100% NPV in the diagnosis of adrenal insufficiency (Table 3). Thus, none of the patients with the peak cortisol ≥ 17.5 μg/dL required hydrocortisone replacement.

Among patients diagnosed as adrenal insufficiency by the above criteria, we next examined the cut-off value of the peak cortisol level after CRH stimulation to distinguish patients who

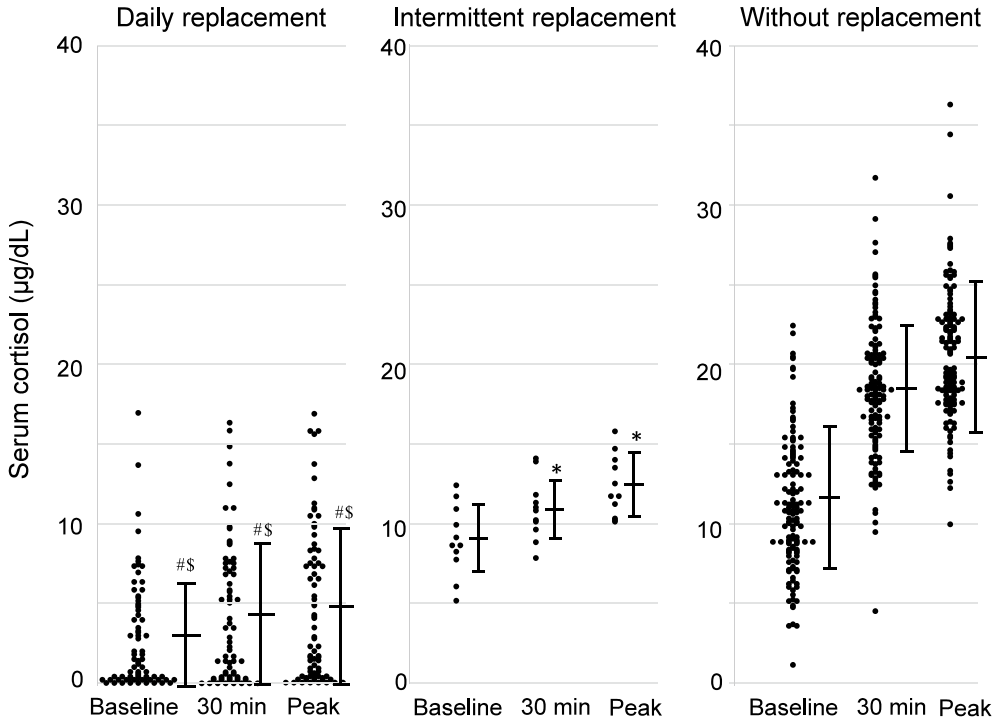

Figure 2. Serum cortisol levels at baseline, 30 minutes and the peak after CRH administration in patients with central adrenal insufficiency.
Patients who required daily, intermittent or no replacement are shown separately.
Values are means +/- SD of 215 patients who underwent CRH test.
*p<0.01, or $p<0.001 vs without replacement
#p<0.001 vs intermittent replacement

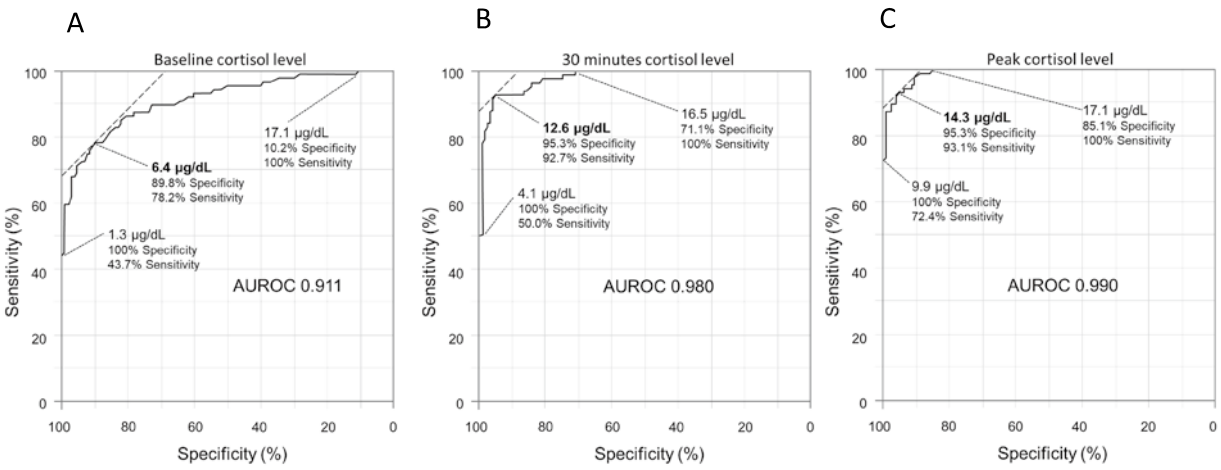

Figure 3. ROC analysis of the cortisol value after CRH test for the diagnosis of central adrenal insufficiency.
ROC analysis of the baseline cortisol (A), 30 minutes cortisol (B) and peak cortisol (C) after CRH test for the diagnosis of central adrenal insufficiency. Optimal cut-off value is shown in bold letters.
AUROC, area under the curve of the receiver operated characteristic

require daily replacement from those who need only intermittent hydrocortisone replacement. The ROC analysis revealed that cut-off value of the peak serum cortisol for those who require daily hydrocortisone replacement was 10.0 μg/dL (100% specificity, 85.5 % sensitivity) with AUROC of 0.916 (Fig 4). However, the diagnostic accuracy of optimal cut-off value (10.0 μg/dL) obtained from ROC analysis was not high (86.2%), and 11 out of 23 patients with the peak cortisol value ≥ 10.0 μg/dL required intermittent hydrocortisone replacement (NPV 47.8%) (Table 4). Nevertheless, it should be noted that all the patients with the peak cortisol < 10 μg/dL required daily hydrocortisone replacement.

Serum DHEA-S level has been shown to be one of the predictive factors and to be better than basal cortisol level for the diagnosis of ACTH insufficiency (11). In the present study, serum DHEA-S levels of patients with central adrenal insufficiency were significantly lower (29.9 ± 45.7 μg/dL) compared to those of patients without adrenal insufficiency (131.8 ± 109.7 μg/dL) (p<0.001). Furthermore, multivariate analysis revealed that serum DHEA-S levels was independently and negatively associated for the hydrocortisone replacement required status (Table 5). When serum DHEA-S data was plotted in each decade of age, only 3 patients without replacement showed serum DHEA-S below the reference range (Fig 5).

Based upon the present retrospective observations using data from final outcomes of patient disposal, an algorithm has

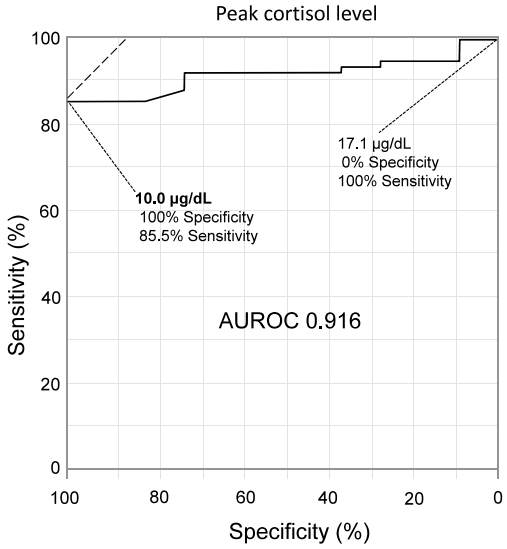

Figure 4. ROC analysis of the peak cortisol after CRH test for distinguishing daily or intermittent supplementation.
Optimal cut-off points are given in bold letters. Peak cortisol levels lower than 10.0 μg/dL after CRH test indicate patients who require daily replacement.
AUROC, area under the curve of the receiver operated characteristic

Table 3. Diagnostic accuracy for predicting the patients with adrenal insufficiency.

Peak Cortisol	Replacement		Total number	PPV (%)	NPV (%)
	Yes	No			
< 17.5 μg/dL	87	22	109	79.8	
≥ 17.5 μg/dL	0	106	106		100
Total	87	128	215		
Sensitivity (%)	100				
Specificity (%)		82.8			
Diagnostic accuracy		89.8%			

PPV ; positive predictive value, NPV ; negative predictive value
Diagnostic accuracy is calculated by the following formula : true positive + true negative / total number x 100

Table 4. Diagnostic accuracy calculated from the proposed criteria for predicting the patients who require daily or intermittent hydrocortisone replacement.

Peak Cortisol	Replacement		Total	PPV (%)	NPV (%)
	Daily	Intermittent			
< 10.0 μg/dL	64	0	64	100	
≥ 10.0 μg/dL	12	11	23		47.8
Total	76	11	87		
Sensitivity (%)	84.2				
Specificity (%)		100			
Diagnostic accuracy		86.2%			

PPV ; positive predictive value, NPV ; negative predictive value
Diagnostic accuracy is calculated by the following formula :
true positive + true negative / total number x 100

been developed for distinguishing patients with central adrenal insufficiency who require daily or intermittent hydrocortisone replacement from those without requirement for replacement (Fig 6). In this proposed algorithm, patients with a suspect of central adrenal insufficiency undergo CRH test and their peak cortisol levels after CRH stimulation were evaluated [Step 1]. If the peak cortisol 17.5 μg/dL or higher, patients can be diagnosed as having normal adrenal function (106 patients, no one requires replacement). If the peak cortisol is < 10.0 μg/dL, daily replacement is recommended (64 patients, all under daily replacement).

Among 45 patients with the peak cortisol at or above 10.0 μg/dL and below 17.5 μg/dL, baseline DHEA-S is evaluated [Step 2]. Among 8 patients who show DHEA-S below the reference range, only one patient required no replacement, one patient is under intermittent replacement, and 6 patients require daily replacement. Among 37 patients who show baseline DHEA-S within the age and sex-based reference range, 6 patients require daily replacement, 10 patients require intermittent replacement, and 21 patients are without replacement. Although the combining evaluation of peak cortisol with baseline DHEA-S tended to determine the requirement for hydrocortisone replacement, borderline patients have to be carefully evaluated using the manual for clinical evaluation about the demand for hydrocortisone replacement (Fig 6) [Step 3].

Table 5. Multivariate analysis of the correlation of various parameter of adrenocortical function with hydrocortisone replacement required status.

	Coeffeicient	SE	T value	95%CI	*p* value
Cortisol baseline	0.004	0.0062	0.654	-0.0082 to 0.0163	NS
Cortisol 30min	-0.007	0.0096	0.831	-0.0269 to 0.0109	NS
Cortisol peak	-0.039	0.0081	4.781	-0.0548 to -0.0228	<0.001
DHEA-S	-0.001	0.0002	4.951	-0.0012 to -0.0006	<0.001

DHEA-S ; dehydroepiandrosterone sulfate, NS ; not significant

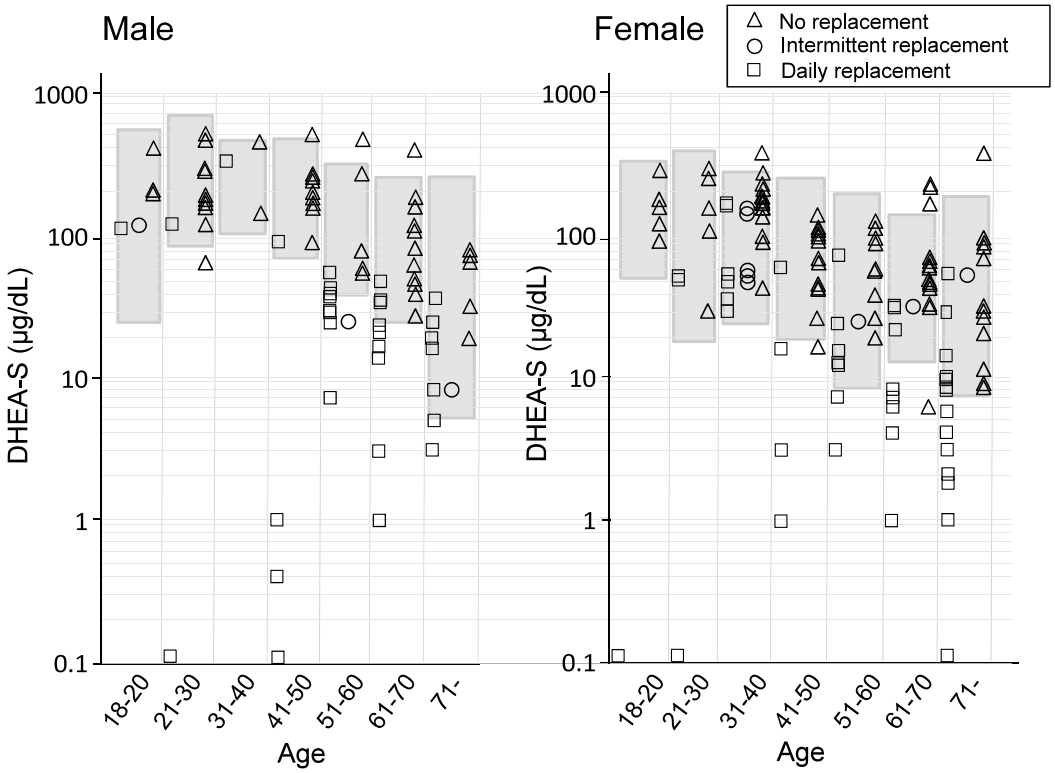

Figure 5. Baseline serum DHEA-S levels in patients who require daily (□), intermittent (○) or no (△) hydrocortisone replacement.
Gray squares indicate reference ranges for each decade of age.

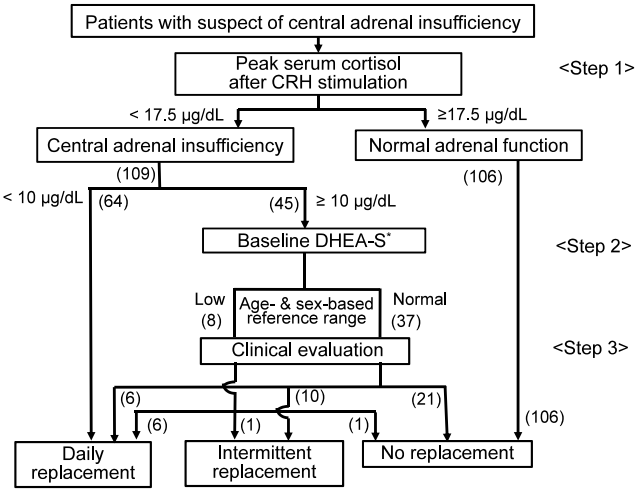

Figure 6. Algorithm for the diagnosis of patients with central adrenal insufficiency who require daily or intermittent hydrocortisone replacement.

DISCUSSION

Many studies have been reported to use stimulation tests for the diagnosis of central adrenal insufficiency (2, 6, 12). Schmidt *et al*. determined cut-off values of basal and peak cortisol after CRH test with the ITT as reference test in 54 patients with suspected central adrenal insufficiency and 20 healthy controls (7), and concluded that CRH stimulation does not bring better diagnostic accuracy as a stimulation test. Maghnie *et al*. compared the diagnostic usefulness of ITT, low and standard dose ACTH test, and CRH test in 24 patients with established diagnosis of growth hormone deficiency, and concluded that none of those tests were reliable for establishing or excluding the presence of central adrenal insufficiency (4). Those studies demonstrated that none of a single stimulation test can give conclusive results in diagnosing central adrenal insufficiency. However, in all those previous studies, the sample sizes were small and the effort of distinguishing patients who require daily from intermittent replacement has not been made.

The present retrospective cohort study involving 215 patients examined the diagnostic performance of CRH test in combination with baseline DHEA-S level. As far as we know, this is the largest study to evaluate the diagnostic performance of CRH test retrospectively not by surrogates such as ITT results, but by patient outcomes. Final decision of requirement for daily or intermittent replacement was made by clinical judgement of symptoms/signs and/or laboratory data of hydrocortisone under- and over-replacement indicating in Figure 7 (13, 14). Based upon those clinical decisions, we went back to find out the cut-off values of CRH test for daily or intermittent hydrocortisone replacement. We propose a cut-off value of 17.5 μg/dL for the peak cortisol level after CRH test for distinguishing normal subjects from patients with central adrenal insufficiency, because none of the subjects with the peak cortisol level at or above 17.5 μg/dL required hydrocortisone replacement. We further propose a cut-off value of the peak cortisol level as 10.0 μg/dL for distinguishing daily from intermittent replacement, because all the subjects with the peak cortisol level below 10.0 μg/dL required daily replacement.

For those patients with the peak cortisol levels at or above 10.0 μg/dL and below 17.5 μg/dL, we adopt baseline DHEA-S values to differentiate patients who require hydrocortisone replacement from those without replacement. However, even after combining serum DHEA-S with CRH test, there were borderline patients for the requirement of hydrocortisone replacement. For those patients, requirement for replacement have to be determined by careful clinical evaluation of the signs and symptoms of patients. In addition, because patients with isolated hypogonadotropic hypogonadism show decreased serum DHEA-S without the presence of adrenocortical insufficiency (15), caution must be taken to use serum DHEA-S for the diagnosis of central adrenocortical insufficiency.

In this report, we propose an algorithm for differential diagnosis of patients who require intermittent or daily replacement. However, because the requirement for hydrocortisone changes depending upon the conditions of patients, such as infection, high fever, injuries and other stressful conditions, we always have to be aware of the fact that the requirement doses or necessity for replacement may change depending upon the conditions of patients. After bearing all those problems in mind, it is important to create a decision-making process in diagnosing and implementing replacement strategy. We hope that the three-step algorithm created from the present retrospective cohort study can improve diagnosis and decision making process for replacement therapy of patients with central adrenal insufficiency.

Limitations of the present study are : first, although the number of patients involved in the study is large, larger number of participants could have stronger statistical power for diagnosing patients who require constant daily or intermittent hydrocortisone replacement therapy. Second, borderline patients need to be evaluated by endocrinologists after analyzing the results of CRH test and baseline DHEA-S in order to decide whether or not they need hydrocortisone replacement. Third, we only evaluated Japanese subjects. However, the present study can help narrow down the number of those patients and reduce the number of misdiagnosis.

In conclusion, we performed a retrospective cohort study and analyzed the relationship of response to CRH and baseline DHEA-S with the requirement for replacement. We have developed an algorithm based upon cut-off values of the peak cortisol after CRH test and baseline DHEA-S to distinguish patients who require daily or intermittent hydrocortisone replacement from those without replacement. However, borderline patients have to be evaluated clinically for the requirement of replacement.

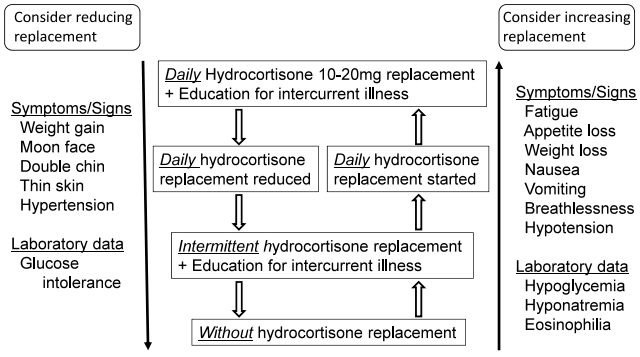

Figure 7. Fine tuning of hydrocortisone doses for replacement based upon clinical evaluation of signs and symptoms.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this study.

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