Efficacy of Using Basal Plasma Adrenocorticotropic Hormone-radioimmunoassay (ACTH-RIA) Level in the Identification of the Cause of Cushing's Syndrome

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Abstract

Basal (8.00 a.m.) plasma ACTH-radioimmunoassay (ACTH-RIA) levels were studied in 32 cases of endogenous Cushing's syndrome (17 Cushing's disease, 13 adrenocortical tumors, and 2 ectopic ACTH syndrome) and 11 normal volunteers. There were overlaps in the ranges of plasma ACTH-RIA levels among patients with Cushing's disease, adrenocortical tumors, and normal volunteers but not ectopic ACTH syndrome. By using different plasma ACTH-RIA levels as cut-off points in differentiating ACTH-dependent from ACTH-independent Cushing's syndrome, the level of 30 pg/ml had the highest diagnostic efficacy with a 94.7 per cent sensitivity, a 84.6 per cent specificity and a 90.6 per cent diagnostic accuracy.

Endogenous Cushing's syndrome results from persistent hypersecretion of cortisol from the adrenal cortex. Its causes are generally classified into adrenocorticotropic hormone (ACTH) - dependent type and ACTH - independent type[1,2]. The ACTH - dependent type includes hypersecretion of ACTH by pituitary tumor (Cushing's disease), hypersecretion of ACTH by non-pituitary tumor (ectopic ACTH syndrome), and rarely hypersecretion of corticotropin-releasing hormone (CRH) by non-hypothalamic tumor (ectopic CRH syndrome). The ACTH - independent type includes adrenocortical tumors (adenoma and carcinoma), and rarely adrenocortical nodular hyperplasia[1-5]. Once Cushing's syndrome is diagnosed, it is necessary to determine its etiology to select the appropriate therapy. This is generally achieved by assessing the results of standard high dose dexamethasone suppression test in combination with plasma ACTH level[1-8]. However, data on plasma ACTH levels in patients with endogenous Cushing's syndrome are limited in Thailand because ACTH assay is less commonly available than assays for other polypeptide hormones. At Siriraj Hospital, we have performed various laboratory investigations including radioimmunoassay of plasma ACTH (ACTH-RIA) in a

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number of patients with Cushing's syndrome of different etiologies. Therefore, we present here our experience in using plasma ACTH-RIA level for identifying the etiology of Cushing's syndrome.

PATIENTS AND METHOD

Thirty-two proven cases of endogenous Cushing's syndrome and 11 normal volunteers were studied. None of them had conditions which were known to interfere with the hypothalamic-pituitary-adrenal function and cortisol metabolism[1,2,5,8]. Cushing's syndrome was diagnosed by the presence of elevated basal (8.00 a.m.) serum cortisol and 24-hour-urine free cortisol (24-h-UFC) concentrations which were non-suppressible with standard 2-day low dose dexamethasone suppression test[1-9]. Among the 32 cases, 17 had Cushing's disease, 13 had adrenocortical tumors, and 2 had ectopic ACTH syndrome. The causes of Cushing's syndrome were diagnosed according to combinations of the following results[1-9]: standard 2-day high dose dexamethasone suppression test, computed tomography (CT) or magnetic resonance imaging (MRI) scan with contrast enhancement of pituitary and/or adrenal glands, histopathological features and therapeutic outcome (Table 1).

Standard dexamethasone suppression tests: The standard 2-day low dose and high dose dexamethasone suppression tests were performed and interpreted according to the method previously described[10-12].

Measurement of plasma ACTH levels: Blood samples were collected in a plastic tube at 8.00 a.m. prior to the standard dexamethasone suppression test. EDTA (7.2 mg/5 ml of whole blood) was used as an anticoagulant. The specimens were immediately transferred to the laboratory and centrifuged at 760 x g for 10 minutes at 4°C. The plasma fraction was collected in a plastic tube containing 500 KIU/ml of Trasylol and kept at -20°C for subsequent ACTH assay.

Analytical methods: ACTH was measured by radioimmunoassay without prior extraction of the plasma samples, using a kit purchased from Incstar Corporation, U.S.A. which possesses the minimum detectable ACTH level of 5 pg/ml. Serum cortisol and urine free cortisol were measured by radioimmunoassay, using a commercial kit purchased from Amersham Corporation, UK.

Statistical analyses: Values were expressed as mean ± standard deviation. The differences between the means of two groups were estimated by Student's *t* test. A p-value of < 0.05 was considered statistically significant.

RESULTS

The patients' characteristics, causes of Cushing's syndrome, basal plasma ACTH-RIA levels, and basal serum cortisol levels and 24-h-UFC before and after dexamethasone suppression test are shown in Table 1 and Table 2. There were overlaps in the ranges of plasma ACTH-RIA concentrations among patients with Cushing's disease (18.5 - 145.0 pg/ml), adrenocortical tumors (5.0 - 42.0 pg/ml), and normal volunteers (14.8 - 69.0 pg/ml) but not ectopic ACTH syndrome (540.0 - 980.0 pg/ml) as shown in Fig. 1. The mean plasma ACTH-RIA level of patients with Cushing's disease (65.2 ± 36.7 pg/ml) was significantly higher than that of the normal volunteers (34.6 ± 15.4 pg/ml; $p < 0.01$). Among the 17 cases of Cushing's disease, 11 (65%) had plasma ACTH-RIA levels within the normal range, whereas, only 6 (35%) had plasma ACTH-RIA levels above the upper normal limit of 69 pg/ml, and none had higher than 150 pg/ml. There was no significant correlation between plasma ACTH-RIA levels and basal serum cortisol ($r^2 = 0.18$, $p = 0.09$) or 24-h-UFC levels ($r^2 = 0.015$, $p = 0.66$) as shown in Fig. 2. In contrast, the patients with adrenocortical tumors had a mean plasma ACTH-RIA level of 19.4 ± 11.7 pg/ml which was significantly lower than that of the normal volunteers ($p < 0.05$) and the patients with Cushing's disease ($p < 0.001$). Among the 13 cases with adrenocortical tumors, only 7 (53.8%) had plasma ACTH-RIA levels of lower than 20 pg/ml, whereas, 12 (92.3%) had lower than 35 pg/ml, the mean value of normal volunteers.

The diagnostic efficacy of using different basal plasma ACTH-RIA levels of 20, 25, 30, 35 and 40 pg/ml as cut-off points in differentiating ACTH-dependent from ACTH-independent Cushing's syndrome are shown in Table 3. The plasma level of 30 pg/ml had highest diagnostic efficacy with a sensitivity of 94.7 per cent, a specificity of 84.6 per cent, a diagnostic accuracy of 90.6 per cent, a positive predictive value of 90.0 per cent, and a negative predictive value of 91.7 per cent.

DISCUSSION

Plasma ACTH determination is generally accepted to be of value in distinguishing ACTH-

Table 1. Patients' characteristics and evidence(s) of definite etiologic diagnosis of Cushing's syndrome.

Case	Age	Sex	Diagnosis	Evidences of definite diagnosis
1	27	M	Cushing's disease *	Pituitary CT scan: microadenoma (9 mm)
2	27	M	Cushing's disease **	Pituitary CT scan: macroadenoma (14 mm) Histopathology: chromophobe adenoma
3	34	F	Cushing's disease **	Pituitary CT scan: macroadenoma (16 mm) Histopathology: chromophobe adenoma
4	50	F	Cushing's disease *	Pituitary CT scan: microadenoma (8 mm)
5	26	F	Cushing's disease *	Pituitary CT scan: microadenoma (6 mm)
6	67	F	Cushing's disease *	Pituitary MRI scan: microadenoma (9 mm)
7	18	F	Cushing's disease **	Pituitary CT scan: macroadenoma Histopathology: chromophobe adenoma
8	57	F	Cushing's disease *	Pituitary CT scan: microadenoma (8 mm)
9	32	F	Cushing's disease **	Pituitary CT scan: macroadenoma (14 mm) Histopathology: pituitary adenoma
10	25	F	Cushing's disease *	Pituitary MRI scan: microadenoma (5 mm)
11	24	F	Cushing's disease **	Pituitary MRI scan: microadenoma (7 mm) Histopathology: pituitary adenoma with positive ACTH staining
12	25	F	Cushing's disease *	Pituitary MRI scan: microadenoma (8 mm)
13	28	F	Cushing's disease *	Pituitary MRI scan: microadenoma (8 mm)
14	32	F	Cushing's disease **	Pituitary MRI scan: microadenoma (10 mm) Histopathology: pituitary adenoma with positive ACTH staining
15	28	F	Cushing's disease **	Pituitary MRI scan: microadenoma (9 mm) Histopathology: pituitary adenoma with positive ACTH staining
16	23	F	Cushing's disease * with adrenocortical nodular hyperplasia	Pituitary CT scan: macroadenoma (15 mm) Adrenal CT scan: enlarged both adrenal glands with left adrenal adenoma Adrenal histopathology: nodular hyperplasia
17	25	F	Cushing's disease * with adrenocortical nodular hyperplasia	Pituitary MRI scan: microadenoma (6 mm) Adrenal CT scan: enlarged both adrenal glands with left adrenal adenoma Adrenal histopathology: nodular hyperplasia
18	29	M	Ectopic ACTH syndrome	Histopathology: mediastinal paraganglioma
19	27	M	Ectopic ACTH syndrome	Histopathology: undifferentiated carcinoma of the liver
20	36	F	Adrenocortical adenoma	Histopathology
21	22	F	Adrenocortical adenoma	Histopathology
22	28	F	Adrenocortical adenoma	Histopathology
23	26	F	Adrenocortical adenoma	Histopathology
24	43	F	Adrenocortical adenoma	Histopathology
25	36	F	Adrenocortical adenoma	Histopathology
26	35	F	Adrenocortical adenoma	Histopathology
27	17	M	Adrenocortical adenoma	Histopathology
28	20	F	Adrenocortical carcinoma	Histopathology
29	22	F	Adrenocortical carcinoma	Histopathology
30	72	F	Adrenocortical carcinoma	Histopathology
31	21	M	Adrenocortical carcinoma	Histopathology
32	27	M	Adrenocortical carcinoma	Histopathology

M Male
F Female
* Clinical and biochemical improvement after pituitary radiation
** Clinical and biochemical improvement after removal of pituitary adenoma

Table 2. Results of standard 2-day high dose dexamethasone suppression test and basal plasma ACTH-RIA levels.

Case	Baseline		Standard DST *		
	Serum cortisol (μg/dl)	24-hour UFC@ (μg/g Cr)	Serum cortisol (μg/dl)	24-hour UFC (μg/g Cr)	Basal plasma ACTH-RIA (pg/ml)
1	28.5	270.0	2.4	64.0	30.0
2	36.2	689.9	17.0	99.0	42.0
3	27.2	136.0	6.8	38.0	69.0
4	17.9	204.0	7.2	39.0	63.0
5	26.5	314.0	8.8	50.0	30.0
6	40.7	1150.5	12.4	416.8	86.0
7	18.0	811.2	3.2	34.1	41.0
8	67.7	406.0	48.9	21.0	103.0
9	40.1	1033.0	27.0	98.0	145.0
10	35.6	912.9	27.2	68.8	18.5
11	35.6	700.8	27.2	68.8	120.0
12	31.4	732.0	18.9	76.0	73.0
13	22.0	293.0	23.3	339.0	39.0
14	45.9	1606.0	30.3	84.0	47.0
15	22.0	431.0	9.8	57.3	30.5
16	16.4	240.0	4.6	44.1	59.6
17	29.3	330.0	25.0	220.0	112.0
18	27.5	910.0	30.0	870.0	980.0
19	39.7	2160.0	37.5	3657.0	540.0
20	22.3	248.9	27.9	254.0	19.5
21	28.4	1632.0	37.2	1301.0	24.5
22	30.5	769.0	30.2	913.0	33.5
23	33.7	2289.4	34.2	1532.3	5.0
24	23.6	409.7	21.6	231.8	7.5
25	36.0	585.7	39.0	792.3	29.5
26	44.0	467.0	35.0	580.0	23.0
27	28.0	2694.0	27.5	1490.0	6.0
28	54.9	2411.0	46.0	7925.0	16.0
29	61.0	1529.0	51.0	1033.0	27.0
30	21.5	234.0	25.3	171.0	9.0
31	24.5	410.0	27.0	827.0	10.0
32	26.3	713.0	30.7	530.0	42.0

* Standard 2-day high dose dexamethasone suppression test
@ 24-hour-urine free cortisol

dependent from ACTH-independent Cushing's syndrome[1-8]. Early studies on the plasma ACTH levels in Cushing's syndrome using bioassays showed that patients with adrenocortical adenoma or carcinoma had undetectable plasma ACTH, whereas, those with bilateral adrenal hyperplasia had high normal or elevated values[13-15]. Although the bioassays are quite specific for ACTH determination, they are not widely used because the technique is complicated, time-consuming, and requires a large volume of blood to obtain accurate results[13,14]. The introduction of radioimmunoassay for ACTH by Berson and Yalow[16] can circumvent the disadvantages of bioassays and enables circulating ACTH to be accurately measured by using only a small amount of plasma. Besser and Landon[17] measured basal plasma ACTH-RIA levels between 8.00-10.00 a.m. in 56 patients with Cushing's syndrome and found that the values in 20 patients with untreated Cushing's disease ranged from 40 to 200 pg/ml with about half of the cases having plasma ACTH-RIA levels within the upper range of 12-60 pg/ml observed in 50 normal subjects. However, the plasma ACTH-RIA values were correlated well with serum cortisol levels with a correlation coefficient of 0.97[17]. Subsequent studies have also

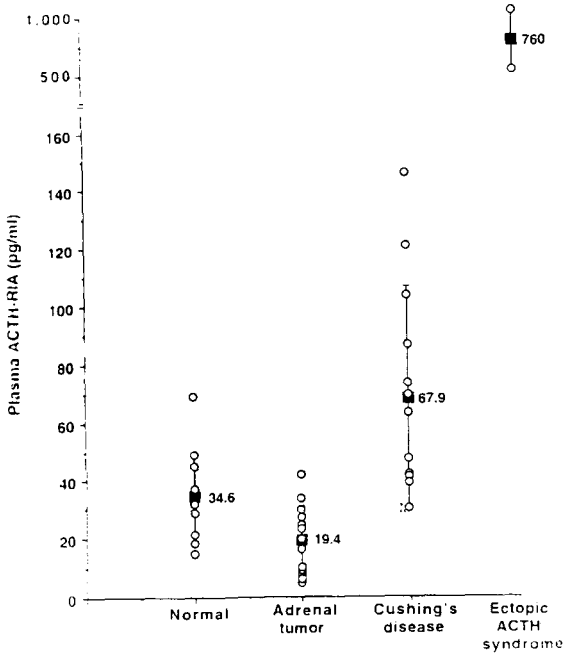

Fig. 1. Basal plasma ACTH-RIA levels in 11 normal volunteers, 13 patients with glucocorticoid producing adrenocortical tumors, 17 with Cushing's disease, and 2 with ectopic ACTH syndrome. Open circle represents an individual basal plasma ACTH-RIA value. Solid square represents a mean basal plasma ACTH-RIA value of each group.

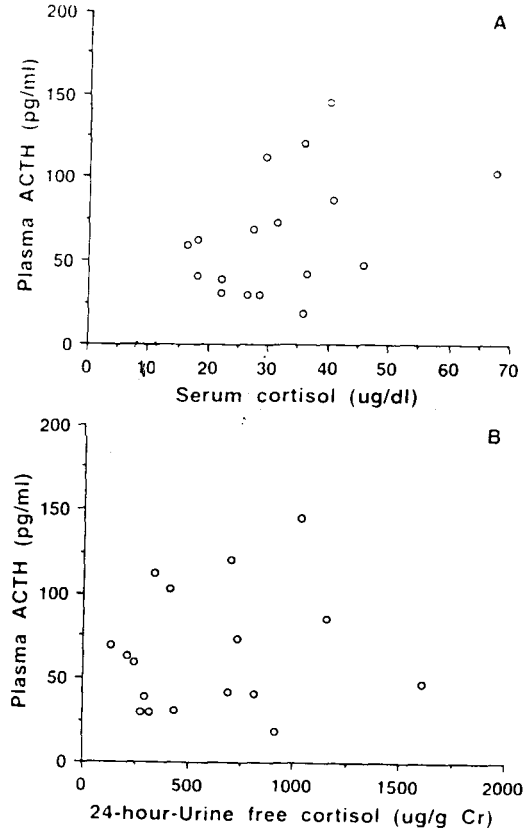

Fig. 2. Relationships between plasma ACTH-RIA levels and basal serum cortisol levels (A) and 24-hour urine free cortisol (B) in 17 patients with Cushing's disease.

Table 3. Efficacy of using different plasma ACTH-RIA levels in differentiating ACTH dependent from ACTH independent Cushing's syndrome *

	Cut-off plasma ACTH-RIA level (pg/ml) *				
	20	25	30	35	40
Sensitivity (%)	94.7	94.7	94.7	78.9	73.7
Specificity (%)	53.8	69.2	84.6	92.3	92.3
False negative (%)	5.3	5.3	5.3	21.1	26.3
False positive (%)	46.2	30.8	15.4	7.7	7.7
Diagnostic accuracy (%)	78.1	84.4	90.6	84.4	81.3
Predictive value (%)					
Positive	75.0	81.8	90.0	93.8	93.3
Negative	87.5	90.0	91.7	75.0	70.6

* Plasma ACTH-RIA values of higher and lower than the indicated cut-off level suggested ACTH-dependent and ACTH-independent Cushing's syndrome, respectively

shown that between one half and two thirds of the patients with Cushing's disease have basal plasma ACTH-RIA values within normal range and the values of the others usually do not exceed 200 pg/ml[5,7,18-22]. In the present study, the ranges of basal plasma ACTH-RIA levels in patients with Cushing's disease and normal subjects as shown in Table 2 and Fig. 1 were similar to those observed by the previous studies[5,17-22]. In addition, the mean plasma ACTH-RIA level in Cushing's disease was significantly higher than the mean normal value. However, the basal plasma ACTH-RIA values were not correlated with basal serum cortisol levels as compared to the study of Besser and Landon[17]. The lack of correlation between plasma ACTH-RIA and serum cortisol levels observed in this study can be explained as follows. Firstly, it is generally known that some patients with Cushing's disease have periodic ACTH secretion[23-26], a single plasma ACTH measurement as done in this study might therefore not accurately assess the relationship between plasma ACTH and serum cortisol levels[1,3,5]. Secondly, the introduction of different RIAs for ACTH using different antibodies against different epitopes of ACTH molecules may result in the discrepancies of the ACTH values between different radioimmunoassays[27]. Thirdly, some pituitary adenomas may secrete various ACTH precursors, so-called "big ACTH"[28]. Therefore, radioimmunoassays for ACTH may fail to detect big ACTH, resulting in inappropriately low plasma ACTH levels when compared to serum cortisol levels[3].

In ectopic ACTH syndrome, plasma ACTH-RIA values of higher than 200 pg/ml have been observed in 50 - 65 per cent of the patients, whereas, the others have the values within normal range[18,20-22,29]. In contrast to the previous studies, the plasma ACTH-RIA of our 2 patients with ectopic ACTH syndrome were extremely high and did not overlap the values observed in Cushing's disease. This was due to the very limited number of patients in this study. The markedly elevated plasma ACTH level has been shown to result from the increased proopiomelanocortin (POMC) gene expression of the tumors producing ectopic ACTH syndrome rather than the increased efficiency in post-translational process of POMC mRNA[30,31].

Several studies using either bioassay[13-15] or RIA[17-22] have shown that, plasma ACTH levels are usually low or undetectable in patients with adrenocortical tumors. The low plasma ACTH levels are due to the negative feed-back control of ACTH secretion by the high level of serum cortisol primarily secreted from the adrenocortical tumors. These findings are similar to those observed in individuals with exogenous glucocorticoid administration[6,16,32]. In the present study, though the patients with adrenocortical tumors had a mean plasma ACTH level significantly lower than that of the normal volunteers, some cases still had plasma ACTH-RIA values within the normal range. This observation is not clearly understood, it can be, however, presumably explained by the presence of circulating ACTH-like molecules or precursors which are not suppressible with the high serum cortisol level produced by the adrenocortical tumor[27].

The overlaps of plasma ACTH-RIA levels among normal subjects, patients with Cushing's disease and adrenocortical tumor observed in this study as well as others leads to the questions whether plasma ACTH-RIA can be used for distinguishing ACTH-dependent from ACTH-independent Cushing's syndrome and at what plasma ACTH-RIA level is the best cut-off point in the differential diagnosis of Cushing's syndrome. In general, the cut-off plasma ACTH-RIA level of 20 pg/ml which is the lower limit of the normal range, is used by many authorities[5-7]. In this study, however, the plasma ACTH-RIA level of 30 pg/ml was the best cut-off point among the levels ranging form 20 - 40 pg/ml. Though, our findings and others have shown that radioimmunoassays for plasma ACTH level are useful in distinguishing ACTH-dependent from ACTH-independent Cushing's syndrome, this method frequently gives overlapped plasma ACTH levels which result in false positive and false negative diagnosis. Several attempts have been introduced to improve the efficacy of plasma ACTH measurement in the differential diagnosis of Cushing's syndrome. The measurement of plasma ACTH-RIA levels later in the day has been shown to be more helpful in the diagnosis of Cushing's disease[1,33]. The recent introduction of immunoradiometric assay (IRMA) for ACTH (ACTH-IRMA) has been shown to measure plasma ACTH more accurately than does the RIA particularly at the low plasma ACTH level[2,27,34-36]. Therefore, plasma ACTH-IRMA is more useful in the diagnosis of a state of suppressed

plasma ACTH level such as glucocorticoid producing adrenocortical tumors[2,35,36]. Nowadays, ACTH-IRMA rather than ACTH-RIA is used by most authorities as the method of choice in the differential diagnosis of Cushing's syndrome[1-3,27]. The measurement of plasma ACTH levels either by RIA or IRMA in response to the CRH stimulation test with or without petrosal sinus sampling has been shown to increase the efficacy in the differential diagnosis of Cushing's syndrome particularly in distinguishing Cushing's disease from ectopic ACTH syndrome[1-5,37-39].

In conclusion, radioimmunoassay for basal plasma ACTH level is a fairly useful method in the etiologic diagnosis of Cushing's syndrome. In the presence of hypercortisolism, a plasma ACTH-RIA level of lower than 30 pg/ml suggests ACTH-independent Cushing's syndrome i.e. cortisol producing adrenocortical tumor, whereas, a value of higher than that limit suggests ACTH-dependent Cushing's syndrome i.e. Cushing's disease or ectopic ACTH syndrome. The presence of extremely high plasma ACTH-RIA level strongly suggests ectopic ACTH syndrome.

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ประสิทธิภาพของการใช้ระดับพลาสม่าแอดรีโนคอร์ติโคโทรปิคฮอร์โมนพื้นฐานซึ่งวัดโดยวิธีเรดิโออิมมูโนแอสเสย์ในการวินิจฉัยแยกสาเหตุของกลุ่มอาการคุชชิ่ง

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คณะผู้วิจัยได้ทำการศึกษาระดับพลาสม่าแอดรีโนคอร์ติโคโทรปิคฮอร์โมน (เอ.ซี.ที.เอช.) พื้นฐาน ที่เวลา 8.00 น. โดยวิธีเรดิโออิมมูโนแอสเสย์ (อาร์.ไอ.เอ.) ในอาสาสมัครปกติ 11 ราย และ ผู้ป่วยกลุ่มอาการคุชชิ่ง 32 รายซึ่งมีสาเหตุจากโรคคุชชิ่ง 17 ราย, เนื้องอกต่อมหมวกไต 13 ราย และ เนื้องอกนอกต่อมใต้สมองที่หลั่งเอ.ซี.ที.เอช. 2 ราย. ผลการศึกษาพบว่ามีการคาบเกี่ยวกันของพิสัยของระดับพลาสม่าเอ.ซี.ที.เอช.–อาร์.ไอ.เอ.ระหว่างผู้ป่วยโรคคุชชิ่ง (18.5–145.0 พิโคกรัม/มิลลิลิตร), ผู้ป่วยเนื้องอกต่อมหมวกไต (5.0–42.0 พิโคกรัม/มิลลิลิตร) และ อาสาสมัครปกติ (14.8–69.0 พิโคกรัม/มิลลิลิตร). ส่วนระดับพลาสม่าเอ.ซี.ที.เอช.–อาร์.ไอ.เอ.ของผู้ป่วยเนื้องอกนอกต่อมใต้สมองที่หลั่งเอ.ซี.ที.เอช.สูงมาก (540.0–980.0 พิโคกรัม/มิลลิลิตร) และ ไม่คาบเกี่ยวกับผู้ป่วยกลุ่มอื่น ๆ รวมทั้งอาสาสมัครปกติ. ในผู้ป่วยโรคคุชชิ่ง มี 6 ราย (ร้อยละ 35) ที่มีระดับพลาสม่าเอ.ซี.ที.เอช.–อาร์.ไอ.เอ.สูงกว่าเกณฑ์ปกติ และไม่มีรายใดเลยที่มีระดับสูงกว่า 150 พิโคกรัม/มิลลิลิตร. นอกจากนี้ระดับพลาสม่าเอ.ซี.ที.เอช.–อาร์.ไอ.เอ.พื้นฐานไม่มีความสัมพันธ์กับระดับซีรั่มคอร์ติซอลพื้นฐานหรือปริมาณคอร์ติซอลอิสระในปัสสาวะ 24 ชั่วโมง. ในผู้ป่วยเนื้องอกต่อมหมวกไต มี 7 ราย (ร้อยละ 53.8) ที่มีระดับพลาสม่าเอ.ซี.ที.เอช.–อาร์.ไอ.เอ.ต่ำกว่า 20 พิโคกรัม/มิลลิลิตร และมี 12 ราย (ร้อยละ 92.3) ที่มีระดับพลาสม่าเอ.ซี.ที.เอช. อาร์.ไอ.เอ.ต่ำกว่า 35 พิโคกรัม/มิลลิลิตรซึ่งเป็นค่าเฉลี่ยของอาสาสมัครปกติ. การใช้ระดับพลาสม่าเอ.ซี.ที.เอช.–อาร์.ไอ.เอ.ที่ 30 พิโคกรัม/มิลลิลิตรจะให้ผลการวินิจฉัยแยกกลุ่มอาการคุชชิ่งชนิดที่ขึ้นกับเอ.ซี.ที.เอช. (ได้แก่ โรคคุชชิ่ง และ เนื้องอกนอกต่อมใต้สมองที่หลั่งเอ.ซี.ที.เอช.) จากชนิดที่ไม่ขึ้นกับเอ.ซี.ที.เอช. (ได้แก่ เนื้องอกต่อมหมวกไต) ดีที่สุดโดยมีความไวร้อยละ 94.7, ความจำเพาะร้อยละ 84.6 และ ความเที่ยงตรงร้อยละ 90.6 นอกจากนี้ระดับเอ.ซี.ที.เอช.–อาร์.ไอ.เอ.ที่สูงมากจะบ่งชี้ถึงเนื้องอกนอกต่อมใต้สมองที่หลั่งเอ.ซี.ที.เอช.มากกว่าโรคคุชชิ่ง.

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