jraas

Journal of the Renin-Angiotensin-Aldosterone System
January-March 2016: 1–6

DOI: 10.1177/1470320315625703
jra.sagepub.com
SAGE

Evaluation of the (1–24) adrenocorticotropin stimulation test for the diagnosis of primary aldosteronism

Ken Terui[1,2], Kazunori Kageyama[1,2], Takeshi Nigawara[1,2], Takako Moriyama[1,2], Satoru Sakihara[3], Shinobu Takayasu[1,2], Yuko Tsushima[1,2], Yutaka Watanki[1,2], Satoshi Yamagata[1,2], Aya Sugiyama[1,2], Shingo Murasawa[1,2], Yuki Nakada[1,2], Toshihiro Suda[3] and Makoto Daimon[1,2]

Abstract

Objective: The purpose of this study was to investigate the diagnostic power of the adrenocorticotropin (ACTH) stimulation test in patients with primary aldosteronism (PA) and those with aldosterone-producing adenoma (APA).

Design: This study was based on a retrospective database analysis.

Subjects and methods: We assessed 158 hypertensive patients with a high plasma aldosterone-to-renin ratio (ARR) including 97 with at least one positive confirmatory test result who did not undergo surgery and comprised a "possible PA" group, 19 with negative results in all tests who were the "non-PA" group, and 41 diagnosed with APA following surgery who were the APA group. The "confirmed PA group" included APA patients and patients from the possible PA group showing both high ARR and hypokalemia. One case was diagnosed as a metastasis.

Results: Receiver-operating characteristic (ROC) analysis showed that the diagnostic accuracy of ACTH test was not very effective in differentiating between APA patients and possible PA and non-PA patients. The optimal cut-off value of maximal plasma aldosterone concentration for differentiating between patient in the confirmed PA group and other patients showed moderate accuracy.

Conclusions: The ACTH test may not be useful as a screening or confirmatory test, but the test may be useful for differentiating between patients with confirmed PA and the rest of the cohort. The positive finding of the ACTH test may at least support a higher likelihood of lateralizing on adrenal venous sampling.

Keywords

Primary aldosteronism, adrenocorticotropin test, aldosterone-to-renin ratio, confirmatory test, adrenal venous sampling

Date received: 20 August 2015; accepted: 7 December 2015

Introduction

Primary aldosteronism (PA) is considered to be the most common cause of secondary hypertension.[1,2] To screen for PA, the plasma aldosterone-to-renin ratio (ARR) is assessed in all hypertensive patients.[3] If the ARR is higher than the normal limit, confirmatory tests are requested, such as the captopril challenge test (CCT), saline infusion test (SIT), furosemide plus upright test (FUT), and oral sodium loading test (OST).

The Endocrine Society advocates the use of four confirmatory tests (CCT, SIT, OST, and fludrocortisone suppression test) in their clinical practice guidelines for PA. A conclusive diagnosis of PA is based on at least one positive test result.[3] The Japan Endocrine Society and the Japanese Society of Hypertension each have guidelines for the diagnosis of PA, both proposing the use of the same three confirmatory tests (CCT, SIT, and FUT). Two positive test

[1]Department of Endocrinology and Metabolism, Hirosaki University Graduate School of Medicine, Japan
[2]Department of Endocrinology and Metabolism, Hirosaki University Graduate School of Medicine, Japan
[3]Aomori Rosai Hospital, Japan

Corresponding author:
Ken Terui, Department of Endocrinology and Metabolism, Hirosaki University Graduate School of Medicine, 5 Zaifu-Cho Hirosaki 036-8562, Japan.
Email: terui@hirosaki-u.ac.jp

results are needed for the diagnosis according to the guidelines of the Japan Endocrine Society,[4] while only one positive test result is needed in the Japanese Society of Hypertension guidelines.[5] There is no consensus on whether any of the confirmatory tests is a "gold standard" or how many tests are needed for the diagnosis.

The adrenocorticotropin (ACTH) stimulation test, which is generally used for the diagnosis of adrenal insufficiency,[6] has been reported to be useful in the diagnosis of aldosterone-producing adenoma (APA) in PA patients.[7] In a Japanese clinical review paper, Omura and Nishikawa proposed that the (1–24) ACTH stimulation test should be a secondary screening test for PA, following the observation of elevated ARR in hypertensive patients. They reported that a cut-off value of maximal plasma aldosterone concentration (Max PAC, ng/dl) to cortisol ratio of 0.85 or greater was useful for the diagnosis of PA.[8] Subsequently, the ACTH stimulation test has been extensively used for the diagnosis of PA in Japan. The test is routine in our hospital. Nevertheless, no validation study has been performed thus far, and the diagnostic power of the ACTH stimulation test remains generally unknown.

The present study aimed to examine whether the ACTH stimulation test shows the same diagnostic power as other confirmatory tests between PA patients and non-PA hypertensive patients and whether the test is useful in the diagnosis of APA in patients with suspected PA. To address this hypothesis, we determined the best cut-off value to evaluate the diagnostic efficiency of the ACTH stimulation test in patients with PA and those with APA.

Patients and methods

Patients

We retrospectively analyzed hypertensive patients with elevated ARR (>20; PAC in ng/dl and plasma renin activity (PRA) in ng/ml/h) (n=158) who were admitted to the Department of Endocrinology, Metabolism and Infectious Diseases of Hirosaki University School of Medicine and Hospital from 2008–2011. The study was approved and registered as an institutional case-notes review at the Institutional Review Board of Hirosaki University School of Medicine and Hospital (Registration No. 2014-240).

Before the determination of ARR, mineralocorticoid receptor blockers, diuretics, beta-adrenergic blockers, angiotensin-converting enzyme inhibitors, and/or angiotensin receptor blockers were withheld for at least two weeks. Only calcium channel blockers and/or alpha-adrenergic blockers were used as antihypertensive therapy. According to the Japanese guidelines, all of the patients underwent at least two of the three confirmatory tests for the diagnosis of PA (CCT, SIT, or FUT) on different days.

Overall, 73 patients had at least two positive test results and 66 had only one positive test result, while 19 had negative results for all two or three tests (non-PA group). Of the 73 patients with two positive test results, 60 underwent adrenal venous sampling (AVS), while the remaining 13 did not undergo AVS because they opted against surgery. Of the 66 patients with one positive test result, 35 desired and underwent AVS. Finally, 38 patients were diagnosed by AVS with a unilateral adrenal lesion, and all of these patients underwent surgical treatment. Further, 57 patients were diagnosed with bilateral adrenal lesions. Because of the presence of a large adrenal tumor, four patients underwent surgery without AVS being performed. Postoperatively, 41 lesions were diagnosed as adrenocortical adenoma by light microscopic examination (APA group), and one lesion was diagnosed as a metastasis from renal cell carcinoma. After surgery, hypertension in 41 patients improved with normalization of ARR. Further, 97 patients (possible PA group) had at least one positive test result but did not undergo any surgery (Figure 1).

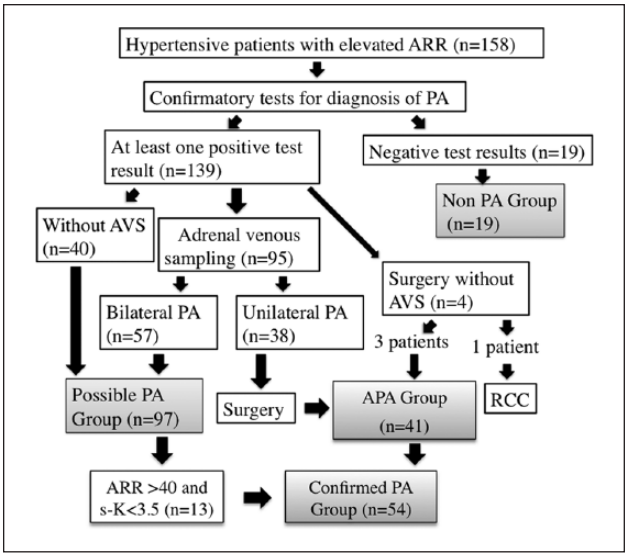

Figure 1. Diagnostic flowchart. APA: aldosterone-producing adenoma; ARR: aldosterone-to-renin ratio; AVS: adrenal venous sampling; PA: primary aldosteronism; PAC: plasma aldosterone concentration; RCC: renal cell carcinoma.

Confirmatory testing

1. CCT: During the test, patients remained in the supine position, and PAC and PRA were measured at 0, 60, and 90 min after the oral administration of captopril (50 mg). The CCT was considered to be positive if the ARR at 60 or 90 min after captopril administration was >20.[4,5,9]
2. SIT: Patients were administered an intravenous drip infusion of 2 l of 0.9% NaCl over 4 h. After infusion, PAC was measured. The SIT was considered to be positive if PAC>6.0 ng/dl.[4,5,9]

Table 1. Characteristics of the study population.

n	Total	APA	Possible PA	Non-PA
	158	41	97	19
Age (years) (median (IQR))	57.0 (47.0–63.8)	53.0 (45.0–59.0)	58.0 (46.0–65.0)	60.0 (55.0–62.5)
Height (cm) (median (IQR))	158.9 (152.0–165.0)	161.8 (155.3–168.8) [a]	158.1 (151.0–164.0)	159.9 (150.5–165.7)
Body weight (kg) (median (IQR))	61.9 (52.3–71.4)	65.4 (53.3–73.6)	61.4 (52.7–71.3)	54.6 (51.8–68.8)
BMI (kg/m^2) (median (IQR))	24.8 (22.2–27.2)	23.6 (20.6–27.1)	25.2 (22.7–27.4)	24.4 (21.5–25.8)
Serum potassium (mmol/l) (median (IQR))	3.7 (3.3–4.0)	3.4 (2.9–3.7)[b]	3.7 (3.6–4.0)	3.9 (3.8–4.2)
PAC (ng/dl) (median (IQR))	14.4 (11.0–20.5)	16.9 (11.4–32.0)	14.0 (10.9–18.2)[c]	13.2 (9.4–19.6)[d]
PRA (ng/ml/h) (median (IQR))	0.3 (0.2–0.5)	0.2 (0.1–0.3)[e]	0.3 (0.2–0.5)	0.4 (0.3–0.7)[d]
ARR (median (IQR))	45.2 (28.5–96.3)	106.0 (54.5–195.0)[b]	43.0 (28.0–75.3)	30.1 (22.5–37.5)

APA: aldosterone-producing adenoma; ARR: aldosterone-to-renin ratio; BMI: body mass index; IQR: interquartile range; PA: primary aldosteronism; PAC: plasma aldosterone concentration; PRA: plasma renin activity.
[a]$p<0.05$ vs possible PA group; [b]$p<0.01$ vs possible PA or non-PA group; [c]$p<0.01$ vs APA group; [d]$p<0.05$ vs APA group; [e]$p<0.05$ vs possible PA or non-PA group.

3. FUT: After maintaining a supine position for at least 30 min, venipuncture was performed for the measurement of basal PRA. A bolus injection of 40 mg furosemide was administered to each patient. Patients maintained an upright posture during the test. At 2 h after furosemide administration, PRA was measured. The FUT was regarded as positive if PRA<2.0 ng/ml/h.[4,5,9]

(1–24) ACTH stimulation test

All 158 patients underwent the (1–24) ACTH stimulation test as a routine examination. After maintaining a supine position for at least 30 min, a bolus injection of 250 μg cosyntropin (synthetic (1–24) ACTH produced by Daiichi Sankyo Co.) was administered to each patient. PAC and plasma cortisol were measured at 0, 30, and 60 min after the injection.

AVS

AVS was performed by expert radiologists to diagnose whether unilateral or bilateral aldosterone-producing lesions was present. AVS was performed with cosyntropin, as previously reported.[4,10,11] When the lateralized ratio (adrenal venous blood aldosterone/cortisol ratio on the high-value side)/(adrenal venous blood aldosterone/cortisol ratio on the low-value side) was at least 2.6 after ACTH administration, a unilateral lesion was considered to be present on the high-value side.

Statistical analysis

All the data are presented as medians with interquartile ranges. We used one-way analysis of variance (ANOVA) followed by post-hoc Student-Newman-Keuls-Test to compare means between groups. Values of $p<0.05$ were considered to indicate statistical significance.

Receiver-operating characteristic (ROC) curve analysis

The diagnostic accuracy of the ACTH stimulation test was assessed with a ROC curve and the area under the ROC curve (AUC_{ROC}). First, we analyzed the diagnostic accuracy of the ACTH test for differentiating between non-PA patients and PA patients diagnosed by confirmatory tests (including both APA and possible PA groups). Second, we analyzed the diagnostic accuracy of the ACTH test in differentiating between APA patients and possible PA and non-PA patients. Because some patients in the possible PA group were expected to have APA, we defined the "confirmed PA group" to include patients from the APA group and those from the possible PA group who showed both high ARR (>40) and hypokalemia (serum potassium<3.5 mEq/l) (Figure 1). Finally, we analyzed the diagnostic accuracy of the ACTH test for differentiating between the confirmed PA group and the rest of the cohort.

Results

Characteristics of the study population

The clinical characteristics of each group are summarized in Table 1. Body weight of the APA patients differed significantly from that of the possible PA patients. Age, height, and body mass index did not differ among the groups. Patients in the APA group showed significantly lower serum potassium levels compared with the patients in the other groups. Further, basal PAC levels and ARR in the APA group were higher than those in the possible PA and non-PA groups.

Positive rates for the three confirmatory tests

The positive rates for CCT and FUT were more than 94% and 97% in the APA group, respectively, while the positive rate for SIT was only about 70%. In the possible PA group, the positive rate of SIT was only 46% (Table 2).

Table 2. Positive rates for each confirmatory test.

n	Total	APA	Possible PA	Non-PA
	158	41	97	19
CCT	69% (64/93)	94% (17/18)	76% (47/62)	0% (0/12)
SIT	47% (42/90)[a]	70% (19/27)[b]	46% (23/50)[b]	0% (0/13)
FUT	80% (113/142)	97% (35/36)	88% (78/89)	0% (0/17)

APA: aldosterone-producing adenoma; CCT: captopril challenge test; FUT: furosemide plus upright test; PA: primary aldosteronism; SIT: saline infusion test.
[a]$p<0.01$ vs CCT or FUT; [b]$p<0.05$ vs CCT or FUT.

Table 3. Results of plasma aldosterone and cortisol concentrations before and after (1–24) adrenocorticotropin (ACTH) stimulation.

Time point	APA	Possible PA	Non-PA
PAC 0 min (median (IQR))	22.0 (9.9–35.1)[a]	10.8 (7.9–14.0)	9.8 (7.4–12.0)
PAC 30 min (median (IQR))	37.2 (27.2–57.2)[a]	28.9 (21.5–35.3)[c]	24.8 (19.6–29.2)
PAC 60 min (median (IQR))	42.8 (29.5–60.1)[a]	29.0 (21.5–35.3)	24.9 (19.1–28.8)
Cortisol 0 min (median (IQR))	8.8 (7.1–11.2)	10.0 (7.2–12.1)	10.6 (8.2–12.6)
Cortisol 30 min (median (IQR))	20.4 (17.8–21.8)[b]	22.1 (20.1–24.2)	21.5 (19.4–23.4)
Cortisol 60 min (median (IQR))	23.8 (20.2–26.9)	25.5 (22.7–27.6)	22.9 (21.1–27.6)
Max PAC (median (IQR))	42.8 (30.0–60.1)[a]	29.7 (23.0–38.4)[c]	25.1 (19.6–29.4)
Max PAC/cortisol (median (IQR))	1.92 (1.21–3.10)[a]	1.26 (0.98–1.60)	1.11 (0.88–1.27)
Delta PAC (median (IQR))	23.5 (16.4–28.9)[a]	18.5 (14.5–26.4)[c]	15.2 (11.7–20.8) [b]

APA: aldosterone-producing adenoma; IQR: interquartile range; Max: maximum; PA: primary aldosteronism; PAC: plasma aldosterone concentration.
[a]$p<0.01$ vs possible PA or non-PA group; [b]$p<0.05$ vs possible PA group; [c]$p<0.05$ vs non-PA group.

ACTH stimulation test

The PAC value at 30 min in the non-PA group was significantly lower than that in the other two groups. In the APA group, the PAC values at 30 min and 60 min were significantly higher compared with those in the other two groups. Max PAC values, Max PAC to cortisol at the same time ratio (Max PAC/CS), and delta PAC values in the APA group were significantly higher than the corresponding values in the other two groups. Further, the Max PAC values and delta PAC values in the possible PA group were significantly higher than those in the non-PA group. The differences in the Max PAC/CS values between the possible PA and non-PA groups were not significantly different (Table 3). In addition, the Max PAC value in the APA group was significantly higher ($p<0.01$) than that in the possible PA and non-PA groups, and the Max PAC value in the possible PA group was significantly higher ($p<0.05$) than that in the non-PA group (Figure 2).

Diagnostic accuracy of the ACTH stimulation test

We analyzed the diagnostic accuracy of the ACTH test for differentiating between non-PA patients and PA patients diagnosed by confirmatory tests (APA and possible PA groups). The AUC_{ROC} of Max PAC was about 0.70, and the optimal cut-off value of Max PAC was >28.8 ng/dl. These results corresponded to a sensitivity and specificity of 64% and 74%, respectively (Figure 3(a)). The Youden-index-based optimal cut-off was the same as above. We analyzed the diagnostic accuracy of the ACTH test for differentiating between APA group and possible PA and non-PA groups. The AUC_{ROC} of Max PAC was about 0.73, and the optimal cut-off value of Max PAC was >36.8 ng/dl. These results corresponded to a sensitivity and specificity of 61% and 75%, respectively (Figure 3(b)). The Youden-index-based optimal cut-off was 41.7 ng/dl, with a sensitivity and specificity of 56% and 82%, respectively.

Finally, we analyzed the diagnostic accuracy of the ACTH test for identifying the confirmed PA group. The AUC_{ROC} of Max PAC was about 0.77, and the optimal cut-off value of Max PAC was >33.3 ng/dl. These results corresponded to a sensitivity and specificity of 76% and 70%, respectively (Figure 3(c)). The Youden-index-based optimal cut-off of Max PAC was 36.8 ng/dl, with a sensitivity and specificity of 65% and 81%, respectively. The Max PAC with 100% specificity was 54.5 ng/dl, and this value corresponded to a sensitivity of 32%.

Discussion

The diagnosis of PA is a challenging problem in this field. Although medical societies have advocated five tests for diagnosis, there is no consensus as to a single, optimal confirmatory test for PA. Nanba et al. investigated the diagnostic significance of confirmatory tests in Japanese

hypertensive patients[9] and reported that the positive rates for CCT and FUT were more than 85% in patients with PA; in contrast, the positive rate for SIT in these patients was much lower (<65%). Our findings are in agreement with their results. Therefore, both CCT and FUT may be considered as optimal tests for diagnosing PA.

The present study was performed to test whether the ACTH stimulation test was useful for differentiating between PA and non-PA hypertensive patients. Some studies have reported that the ACTH stimulation test is useful for diagnosing PA. For example, Kem et al. reported that PAC levels after ACTH infusion in patients with PA were significantly higher compared with those in patients with essential hypertension.[12] In a clinical review paper, Omura and Nishikawa proposed a cut-off value of Max PAC/CS ⩾0.85 for diagnosing PA.[8] In our study, no significant difference was noted for Max PAC/CS between the possible PA and non-PA groups, as shown in Table 3. On the other hand, Max PAC appeared to be more useful for differential diagnosis than Max PAC/CS. However, in the present study, the optimal cut-off value of Max PAC (>28.8 ng/dl) showed a low accuracy. Thus, the ACTH stimulation test was not adequately sensitive or specific for differentiating between PA and non-PA hypertensive patients.

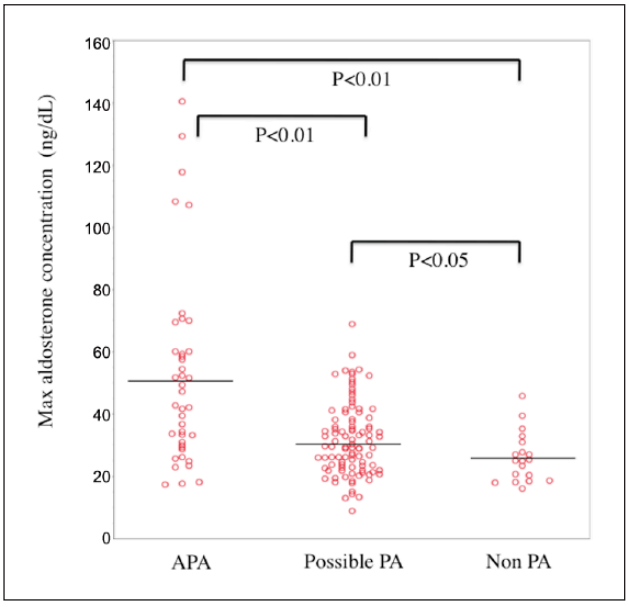

Figure 2. Scattergram of the maximum serum aldosterone concentrations in the aldosterone-producing adenoma (APA), possible primary aldosteronism (PA), and non-PA groups after (1–24) adrenocorticotropin (ACTH) stimulation.

The two major subtypes of PA are APA and idiopathic hyperaldosteronism (IHA).[11] After diagnosing PA, the subtype needs to be identified. In IHA patients, hypersecretion of aldosterone usually occurs from both adrenal glands. Currently, AVS is the only "gold standard" test to distinguish between unilateral and bilateral PA.[7,13] In order to identify PA patients, AVS is a reliable test, but it is an invasive, risky, and costly procedure.[7] Therefore, alternative methods of diagnosis are required. Reincke et al. reported that APA is generally more sensitive to ACTH compared with IHA owing to the expression of ACTH receptors on APA.[14] Several reports, however, have demonstrated that ACTH stimulation leads to an increase in PAC values in some cases of IHA.[11] Dexamethasone (Dex) is used in order to eliminate the action of endogenous ACTH. Sonoyama et al. reported that by combining it with 1 mg Dex suppression, the ACTH stimulation test was useful in the diagnosis of APA among hypertensive patients with suspected PA, with the optimal cut-off value of PAC being >37.9 ng/dl at 90 min after ACTH injection.[7] Recently, Jiang et al. also reported that the ACTH stimulation test with 1 mg Dex suppression was useful for differentiating patients with unilateral PA from patients with bilateral PA, with the optimal cut-off value of PAC being >77.9 ng/dl at 120 min after ACTH injection.[15] In these two studies, 1 mg Dex

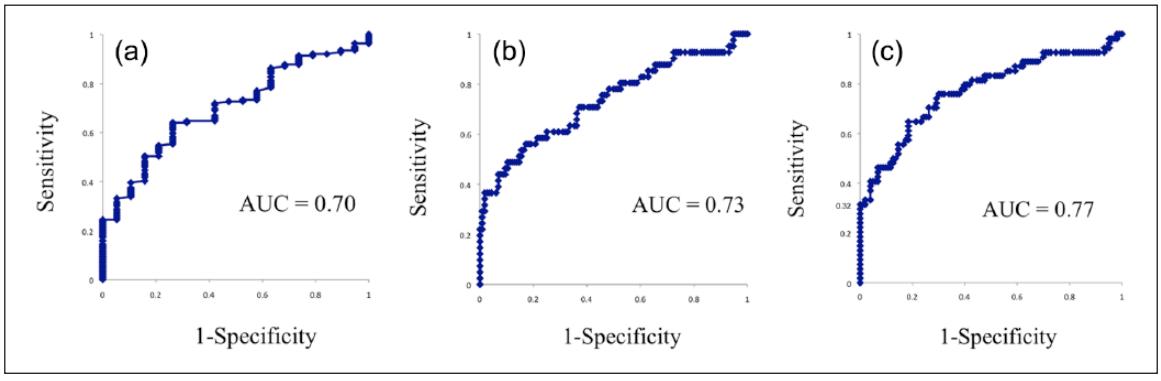

Figure 3. Receiver-operating characteristic (ROC) curves for maximum plasma aldosterone concentration (PAC) of (1–24) adrenocorticotropin (ACTH) stimulation tests. (a) ROC curve for differentiating aldosterone-producing adenoma (APA)/possible primary aldosteronism (PA) groups and non-PA group; (b) ROC curve for differentiating between APA group and possible PA/non-PA groups; (c) ROC curve for differentiating between confirmed PA group and all other patients. AUC: area under the curve.

was used to eliminate the action of endogenous ACTH. However, the authors could not clarify whether Dex suppression was absolutely necessary for such differentiation. Therefore, in our study, we analyzed the diagnostic accuracy of the ACTH stimulation test without Dex suppression for differentiating between APA patients and other patients. In our study, the optimal cut-off value of Max PAC for differentiating between the APA group and other patients was >36.8 ng/dl, showing moderate accuracy.

While computed tomography (CT) is used for diagnosing adrenal tumors, it often falls to diagnose these lesions[10,16] because APAs frequently measure less than 1 cm in diameter. Furthermore, it is very difficult to differentiate between bilateral APA patients and bilateral IHA patients. In the present study, it was likely that some patients from the possible PA group may have had APAs. If such patients can be accurately excluded from the possible PA group and included in the APA group, the diagnostic power between the APA group and other patients might show higher accuracy. We therefore defined a "confirmed PA group" that included patients from the APA group and patients from the possible PA group with both high ARR and hypokalemia. With this classification, the optimal cut-off value of Max PAC was >33.3 ng/dl and showed moderate accuracy. Thus, the (1–24) ACTH stimulation test without combined Dex administration showed moderate diagnostic power compared with the test with Dex. The Max PAC with 100% specificity was 54.5 ng/dl, while this value will show a poor sensitivity of 32% (Figure 3(c)). Therefore, the ACTH test would not be useful for a part of routine screening tests. The positive finding of the ACTH test may at least support a higher likelihood of lateralizing on AVS, and it might be performed in limited patients, for example, the patients who really would not like to have AVS.

Some limitations of our study should be mentioned. This study was a retrospective analysis, and recall bias cannot be excluded. We also used the diagnostic criteria of Japanese guidelines in Japanese patients. Additional studies are needed for clarifying the usefulness of the ACTH stimulation test in other populations.

In conclusion, both CCT and FUT may be considered as optimal tests for diagnosing PA, while the ACTH stimulation test was not adequately sensitive or specific as a screening or confirmatory test for PA. In contrast, the ACTH stimulation test may be useful for differentiating between patients with confirmed PA and the rest of the cohort. The positive finding of the ACTH test may at least support a higher likelihood of lateralizing on AVS, and it might be performed in limited patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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