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Bilateral aldosterone-producing adenomas: differentiation from bilateral adrenal hyperplasia

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Summary

Background: Primary aldosteronism (PA) is a common curable disease of secondary hypertension. Most such patients have either idiopathic bilateral adrenal hyperplasia (BAH) or unilateral aldosterone-producing adenoma (APA). Bilateral APAs are reportedly extremely rare.
Aim: To compare the distinctive characteristics, clinical course, and outcomes of bilateral APA vs. BAH.
Design: Retrospective record review.
Methods: From July 1994 to Jan 2007, 190 patients diagnosed with PA underwent surgical intervention at our hospital. Bilateral APA was diagnosed in 7/164 patients with histologically-proven APA. Twenty-one patients diagnosed as BAH, and 21 randomly selected of unilateral APA patients, matched by age and sex served as controls.
Results: Patients with bilateral APA had similar blood pressure, arterial blood gas analysis, spot urinary potassium to creatinine ratio and clinical symptoms to those with BAH, but lower serum potassium levels ($p=0.027$), lower plasma renin activity ($p=0.037$), and higher plasma aldosterone concentrations ($p=0.029$). Aldosterone-renin ratio (ARR) after administration of 50 mg captopril was higher in bilateral APA than in BAH patients ($p=0.023$), but not different between unilateral APA and BAH ($p=0.218$). A cut-off of ARR >100 ng/dl per ng/ml/h and plasma aldosterone >20 ng/dl after captopril significantly differentiated bilateral APA from BAH. Bilateral subtotal adrenalectomy normalized blood pressure and biochemistry in all patients with bilateral APA.
Discussion: Bilateral APA, presenting simultaneously or sequentially, may not be a rare disease, accounting for 4.3% of APA in this sample. The clinical presentations of bilateral functional adenoma are not different from BAH, but patients with low serum potassium and ARR >100 after captopril should be carefully evaluated for bilateral adenoma.

Introduction

Primary aldosteronism (PA), a common curable disease of hypertension,[1] is characterized by inappropriate production of aldosterone, regulated in part independently of the renin-angiotensin system. The wide application of the plasma aldosterone-to-renin activity (ARR) test for screening hypertensive patients has resulted in the reporting of a much higher prevalence of this disease (up to

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11.2%) in newly diagnosed hypertensive patients.[2] Idiopathic bilateral adrenal hyperplasia (BAH) and aldosterone-producing adenomas (APAs) are the leading causes of PA. Unilateral adrenalectomy is the traditional therapeutic option for APAs, and aldosterone antagonists usually bring about satisfactory blood pressure (BP) control in patients with BAH.[3] The correct diagnosis of surgically correctable forms of PA is therefore of great importance.

However, this syndrome has considerable phenotypic heterogeneity, with diagnostic variants differing from the more typical forms by their responsiveness to angiotensin II. For example, primary adrenal hyperplasia is an uncommon subtype of a unilateral adrenal lesion, and is characterized by a morphological resemblance to BAH, but responds to physiological manoeuvres and unilateral adrenalectomy similar to APA.[4] Nodular adrenal hyperplasia may mimic the biochemical characteristics of an APA, and resolution of hypokalaemia and hypertension occurs after unilateral adrenalectomy.[5] Such paradoxical characteristics may confuse the diagnosis of the subtypes of PA.

Bilateral APAs (BiAPAs) have been rarely reported.[6–10] The clinical manifestations and outcomes of this subtype of PA still present a scenario not well-addressed in the literature. Whether a diagnostic ambiguity exists in the differentiation between bilateral APA and BAH is thus important to determine. We present seven cases of BiAPAs, with a distribution of 4.3% of APA. The distinctive characteristics, clinical course, and outcomes of BiAPAs as compared to BAH are presented.

Methods

Patients

From July 1994 to January 2007, 190 patients with PA underwent surgery at the National Taiwan University Hospital. The histological diagnosis of APA was made in 164 patients, nodular hyperplasia in 16 patients, and BAH in 10 patients. Twenty-one patients diagnosed as BAH (7 patients histologically proved, 14 patients of clinical diagnosis) and randomly selected 21 patients with histologically proved unilateral APAs (UniAPAs), paired by age and sex, were enrolled for comparison. Most of them were referred to a hypertension clinic for the confirmation of PA because of difficulty in BP control (72.3%), hypokalaemia (61.6%), 'incidentalomas' (5.6%), or a positive screening test before discontinuing antihypertensive medications (73.7%). Patients with an ARR >30 (ng/dl per ng/ml/h) and a plasma aldosterone concentration (PAC) >10 ng/dl (>277 pmol/l) were suspected of PA and underwent further evaluation. Before surgery, patients were hospitalized for a comprehensive study of the subtypes of PA. Patients with BAH were assessed in the same centre at the same time.

Confirmatory studies

Prior to surgery, all patients with aldosteronism were studied in our unit as in-patients, according to standardized protocols. Therapy was discontinued for at least 10 days, except for non-dihydropyridine calcium antagonists and alpha-blockers, when required.[1,11] No patient in this series used spironolactone or diuretics before confirmed test. Agents known to interfere with the renin-aldosterone axis, such as steroids, sex hormones, liquorice, or non-steroidal anti-inflammatory drugs, were also withheld. Urine was collected for 24 h on the first day of hospitalization. Two tests were performed on the following two consecutive days: the postural change test[1] and the captopril test.[12] All subjects consumed a normal diet, with sodium *ad libitum*. Biochemical data and blood gas analyses were collected.

On the day of the postural change test, patients were asked to lie in bed overnight; the first blood sample for PRA and PAC was taken at 8 am and the second sample was taken at 12 pm, after four hours of ambulation and upright posture. On the next day, two blood samples were obtained from patients in a supine position before and 1 h after the administration of 50 mg captopril orally. An ARR >30 (ng/dl per ng/ml/h) with a PAC >10 (ng/dl) after administration of captopril was defined as positive for PA. A strict ARR was defined as ARR >100 (ng/dl per ng/ml/h) and a PAC >20 (ng/dl).[13] The concentration of aldosterone was measured by RIA with commercial kits (Aldosterone Maia Kit, Biochem Immunosystems), as previously described.[1,14] The limit of detection of this assay is 10.0 pg/ml at 90% confidence interval. Normal range of aldosterone is 35–300 pg/ml in the upright position. PRA was measured as the generation of angiotensin I *in vitro* using a commercially available RIA kit (Incstar). Normal range for PRA is 2.63 ± 1.32 ng/ml/h in the upright position.

Subtype studies

All patients underwent an intravenous, contrasted computer tomography (CT) scan of the abdomen with thin (3 mm) cuts through the adrenal glands. Dexamethasone suppression adrenocortical scintigraphy (DSS; NP-59, [I-131]6-beta-iodomethyl-norcholesterol) was performed for those with

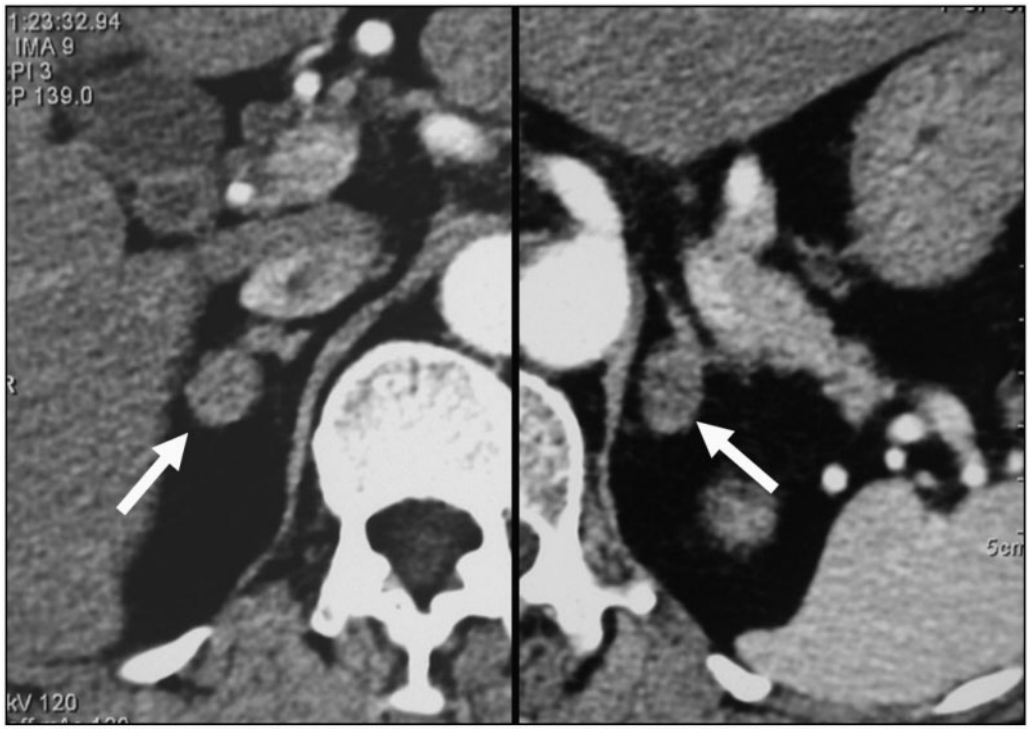

Figure 1. CT scan demonstrating bilateral aldosterone-producing adenomas (arrows) in patient 3, in whom the adenomas were found simultaneously.

suspicious bilateral lesions.[2,11] Briefly, dexamethasone was administered 8 mg daily, starting 3 days before NP-59 injection, and continued throughout the scanning period. Scans were considered positive for adenoma when early (<5 days after NP59 injection) unilateral visualization of the adrenal gland was seen.[15] Adenomas were diagnosed when an adrenal tumour was observed in the contrast-enhanced CT scan. A positive CT finding of an APA was defined by the presence of single nodular lesions (usually hypodense) of at least 10 mm in diameter in the presence of normal surrounding tissue (Figure 1).[16,17] The adrenal CT scan was judged compatible with hyperplasia when any area thicker than 10 mm was detected.[18]

A positive postural test was defined by an ambulatory PAC 30% greater than that of the supine baseline level.[3,11,19] Bilateral adrenal venous sampling (AVS) for aldosterone and cortisol concentrations was offered to patients with a negative (normal) scan or other abnormal scan findings.[20] Blood samples were obtained from the inferior vena cava (IVC) and the right and left adrenal vein. Diagnoses of APA were based on the assumption that a serum aldosterone-to-cortisol ratio from one adrenal of at least two folds the ratio from the other adrenal gland, and the non-dominant normalized aldosterone would be less than or equal to the normalized aldosterone in the IVC.[21] For the diagnosis of BAH, the normalized aldosterone in each adrenal vein had to be equal to or greater than the normalized aldosterone from the IVC.[22] The diagnosis of BAH was based on the combination of the biochemical and hormonal criteria described above and a CT scan or DSS image, but rather bilateral micronodular hyperplasia or apparently normal glands. Patients were diagnosed as BAH if (i) their CT scans showed thickening of bilateral adrenal gland and had bilateral uptakes on DSS study, or (ii) AVS study without lateralization, and had a positive postural study. All our patients with BAH, who were not operated upon, were clinically followed-up every 3 months for at least 4 years without evidence of lateralization.

Histopathological studies

Histological diagnosis of APA was based on well-defined, encapsulated tumours, predominately consisting of foamy clear cells.[3,23] Adenomas appear as nodules of clear cells in sheets or nests that are sharply demarcated by a pseudocapsule, and are compressing the non-neoplastic uninvolved adrenal gland[24] without diffuse thickening of the zona glomerulosa or hyperplastic nodules.[5] Adenomas are differentiated from nodular adrenal hyperplasia by their solitary and well-circumscribed nature.[5,24] Adrenal glands from BAH are marked by a diffuse

hyperplasia of cells resembling those of normal zona glomerulosa without macro- or micronodules (Figure 2).[5]

Clinical outcomes

Clinical outcomes of surgery were assessed for all patients with PA, and categorized based on post-operative resolution of hypokalaemia and hypertension, which were obtained from the final follow-up records. We considered hypertension to be cured if the BP decreased to 140/90 mmHg or less after adrenalectomy, and antihypertensive medications were not required. Hypokalaemia was considered resolved if serum potassium levels remained normal without potassium supplementation.

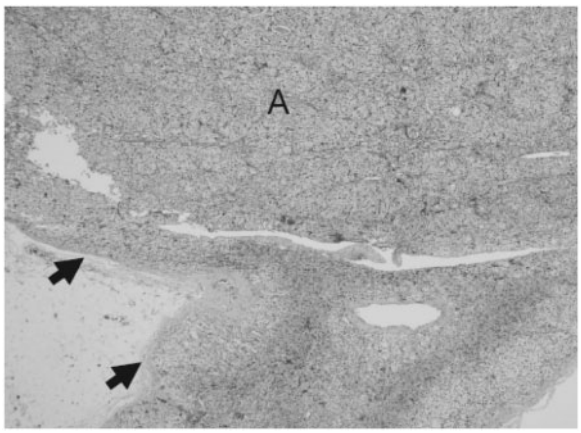

Figure 2. Histopathological findings in patient 4. Microscopic appearance is characterized by uniform adenoma cells (**A**) A well-encapsulated adenoma was observed, and was compressing the non-neoplastic adrenal gland (arrows) in the resected specimen. Haematoxylin and eosin stain, original magnification: 40×.

Statistical analyses

The clinical characteristics of patients with BiAPAs were compared with those of patients with BAH or UniAPAs using SPSS, version 12.0. All results are expressed as means ± SEM. Qualitative criteria were compared using Fisher's exact test. Continuous data were analysed with the two-tailed Mann-Whitney U test. The receiver operating characteristic curve (ROC) was plotted to differentiate patients with BiAPAs from those with BAH using the post-captopril ARR value. A p value of <0.05 was considered to indicate statistical significance.

Results

Clinical characteristics and biochemistry

The clinical characteristics and biochemical data of patients with BiAPAs, UniAPAs and BAH are shown in Table 1. The duration of hypertension before the diagnosis of PA did not differ between patients with BiAPAs and BAH. The BP, pH, HCO_3^-, and spot urinary potassium-to-creatinine ratios were

Table 1 Demographic and baseline clinical data of patients with primary aldosteronism

	Group			p	
	BAH	BiAPAs	UniAPAs	BiAPAs vs. BAH	BiAPAs vs. UniAPAs
Patients	21	7	21	NA	NA
Male gender (%)	9 (42.9)	2 (28.6)	8 (38.1)	0.419	NA
Age (years)	49.7 ± 2.73	51.4 ± 3.6	49.4 ± 7.5	0.796	NA
BMI (kg/m^2)	25.4 ± 0.7	23.3 ± 1.1	26.4 ± 4.6	0.246	0.051
Duration of HTN (years)	11.4 ± 2.1	7.7 ± 1.6	8.8 ± 6.0	0.461	0.810
sBP (mmHg)	155 ± 4	154 ± 11	153 ± 15	0.678	0.890
dBP (mmHg)	92 ± 3	93 ± 5	90 ± 13	0.917	0.696
Potassium (mmol/l)	3.57 ± 0.13	3.08 ± 0.15	3.34 ± 1.01	0.027	0.664
PAC (ng/dl)	39.4 ± 5.7	83.7 ± 25.0	61.6 ± 39.0	0.029	0.168
PRA (ng/ml/h)	0.81 ± 0.26	0.10 ± 0.06	0.31 ± 0.34	0.037	0.184
pH	7.39 ± 0.01	7.44 ± 0.02	7.43 ± 0.07	0.130	0.999
Spot [urine potassium:urine creatinine (mmol/mmol)]	4.14 ± 1.59	4.31 ± 1.36	4.60 ± 1.71	0.999	0.720

BiAPAs, bilateral aldosterone-producing adrenal adenomas; BAH, bilateral adrenal hyperplasia; HTN, hypertension; BMI, body mass index; sBP, systolic blood pressure; dBP, diastolic blood pressure; NA, not applicable; UniAPAs, unilateral aldosterone-producing adenomas. p values were obtained using Mann-Whitney U test for median values. Patients were withdrawn from antihypertensive medications at least 10 days before the study, with the exception of alpha-blockers.

also similar between the two groups. The common symptoms exhibited by these patients were: palpitations, headaches, polyuria, and nocturia; the frequencies of these symptoms did not differ between the two groups.

Patients with BiAPAs had a lower potassium level than those with BAH (3.08 ± 0.15 vs. 3.57 ± 0.13 mEq/dl, $p = 0.027$). The baseline PAC levels of patients with BiAPAs were higher ($p = 0.029$), and PRA were lower, than in patients with BAH ($p = 0.037$). Baseline PAC, PRA and potassium were similar between BiAPAs and UniAPAs.

Patients with bilateral APA

Obvious adenomatous lesions of both adrenal glands were observed on the CT scans of four patients when the diagnosis of PA was made (patients 1–4, Table 2). The size of the lesions was >10 mm (range 12–20 mm; mean 15 mm; Figure 1). The DSS demonstrated bilateral tracer uptakes in all four patients. Bilateral subtotal adrenalectomy was performed to remove the bilateral adenomas, and BP returned to normal in all four patients 21 months after surgery without medication, as did the ARR and serum potassium levels.

The remaining three patients had unilateral adrenal adenomas on their initial CT scans, but one patient had bilateral tracer uptakes observed on DSS (patient 6). A selective adrenal venous sampling in this patient revealed hyperfunctioning of the right adrenal gland; the PAC (ng/dl)/cortisol (μg/dl) levels for the right adrenal, IVC, and left adrenal veins were, respectively, 332.5/12.8, 19.7/16.9 and 35.1/18.8. The AVS showed lateralization in the other two patients. These three patients underwent unilateral adrenalectomy and histology demonstrated APAs that were 20, 15 and 15 mm in size, respectively. After the first surgical procedure, serum potassium levels and systolic BP returned to normal (4.6 ± 1.2 mmol/l and 127 ± 3 mmHg, respectively) despite an elevated ARR (390 ± 192 ng/dl per ng/ml/h) during the subsequent 6 months.

The diagnosis of an APA of the contralateral adrenal gland was made 18 months after unilateral adrenalectomy in two patients and after 48 months in one patient. The CT scans showed adenomas involving the contralateral adrenal glands, 10, 12 and 15 mm in size, respectively. Subtotal adrenalectomy of the remaining adrenal gland was performed on two patients (patients 5 and 7). After the secondary operation, patients 5 and 7 had normal levels of systolic BP (118 and 124 mmHg), serum potassium (4.7 and 5.9 mmol/l), and ARR (2.03 and 6.02 ng/dl per ng/ml/h). For the patient who did not undergo the second procedure, two antihypertensive agents were used to control her blood pressure.

Table 2 Demographic and clinical characteristics of patients with bilateral aldosterone-producing adenomas

Patient	Age	Gender	CT (L/R)	DSS (L/R)	Pre-op K[a]	Pre-op medication[b]	Post-op medication[b,c]	Aldosterone (ng/dl)[a]	Renin (ng/ml/h)[a]	ARR[a]	Notes
1	52	M	+/+	+/+	2.77	1	0	75.8	0.27	280.7	–
2	46	F	+/+	+/+	2.4	2	0	67.2	0.01	6720	–
3	67	F	+/+	+/+	3.2	2	0	76.6	0.48	159.6	–
4	59	M	+/+	+/+	3.14	2	0	56.6	0.01	5660	–
5	47	F	+/−	+/−	3.2	4	0	36.7	0.28	131.1	R adenoma noted 1.5 years after L adrenalectomy, AVS
6	38	F	−/+	+/+	3.2	3	2	38.7	0.32	122	L adenoma noted 1.5 years after R adrenalectomy, AVS
7	54	F	+/−	+/−	3.6	3	0	36.5	0.3	246	R adenoma noted 4 years after L adrenalectomy, AVS

L, left; R, right; Preop, pre-operative; Post-op, post-operative; K, potassium; DSS, dexamethasone suppression scinitigraphy; ARR, aldosterone-to-renin ratio; AVS, adrenal venous sampling; CT, computer tomography. [a]Patients were withdrawn from antihypertensive medications at least 10 days before the study, except for alpha-blockers. [b]Number of antihypertensive drugs taken by each individual. [c]Medication after first adrenalectomy.

The clinical outcomes of all patients were ascertained from the final follow-up records at a mean of 4.2 years from the last surgical procedure. The systolic BP (125 ± 1 mmHg), diastolic BP (84 ± 8 mmHg), and potassium level (4.45 ± 1.08 mmol/l) were improved after bilateral laparoscopic partial adrenalectomy in six patients without antihypertensive agents. After clinical evaluation, the first-degree relatives of BiAPA patients did not show the possibility of aldosteronism.

Patients with UniAPAs

Twenty-one controls with UniAPAs were selected at random from the operated PA population and matched to the BiAPA patients by age and sex. Identification of APA fitted all the strict criteria proposed by Rossi *et al.*[2]: (i) lateralization of aldosterone secretion at AVS ($n=4$), or evidence of lateralized uptake of NP-59 at dexamethasone-suppressed adrenocortical scintigraphy ($n=9$); (ii) pathology ($n=21$); (iii) surgery ($n=21$); and (iv) hypertension cure ($n=15$) or improvement ($n=6$) at follow-up after adrenalectomy.

Patients with BAH

Among the 21 patients with the diagnosis of BAH, seven underwent unilateral adrenalectomy because of unilateral adrenal lesions and negative postural change tests. Five of them have persistent hypertension and high ARR at a mean of 3.9 years after operation. Fourteen patients who did not undergo a surgical procedure had bilateral hyperplasia of the adrenal glands noted on CT scan. Among these 14 patients, eight had bilateral DSS uptakes and six had positive results from a postural study. AVS in these six patients did not show lateralization. The post-captopril ARR in the BAH patients was 299 ± 93 (ng/dl per ng/ml/h; Figure 3).

Differences in the renin-aldosterone axis between patients with PA

Twelve (57.1%) patients with BAH had a positive postural change test, compared with only one patient with BiAPAs ($p=0.060$; Table 3, Figure 3). The PAC after ambulation increased by 3.9 ± 16.2% and 54.9 ± 21.7% ($p=0.208$) for patients with BiAPAs and BAH, respectively. Patients with BiAPAs had a higher ARR than patients with BAH

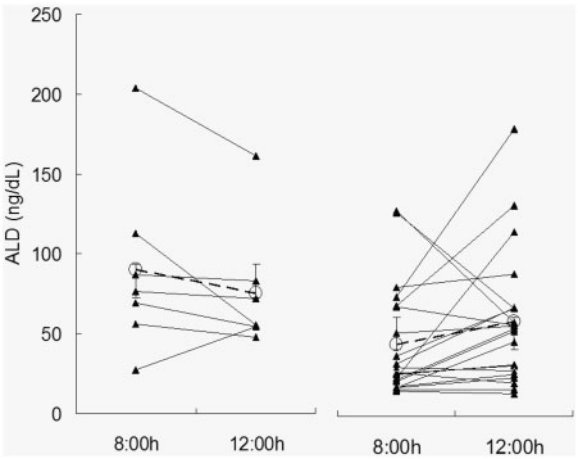

Figure 3. Plasma aldosterone response to 4 h ambulation in seven patients with bilateral aldosterone-producing adenomas (left panel) and 21 patients with idiopathic bilateral adrenal hyperplasia (right panel). Mean (±SEM) responses are also shown (interrupted line).

Table 3 Captopril and postural change tests in patients with primary aldosteronism

	Group			*p*	
	BAH ($n=21$)	BiAPAs ($n=7$)	UniAPA ($n=21$)	BiAPAs *vs.* BAH	BiAPAs *vs.* UniAPAs
ARR before discontinuing medications	668.8 ± 234.9	1955.2 ± 1100.4	770.4 ± 1181.3	0.155	0.116
ARR after discontinuing medications	475 ± 308	1044 ± 764	1373.4 ± 2220.5	0.101	0.979
ARR post-captopril test	292.1 ± 94.2	2126.4 ± 1130.0	444.7 ± 566.5	0.023*	0.351
ARR post-postural test	1128.1 ± 636.1	1193.5 ± 478.7	1582.3 ± 4104.3	0.157	0.999
After captopril (ARR >30)[a] (*n*)	15 (71.4%)	7 (100%)	21 (100)	0.144	NA
After captopril (ARR >100)[b] (*n*)	8 (38.1%)	7 (100%)	13 (61.9)	0.005*	0.075
Positive postural test[c]	12 (57.1%)	1 (14.3%)	5 (23.8)	0.060	0.999

ARR, aldosterone-to-renin ratio; BAH, bilateral adrenal hyperplasia; BiAPAs, bilateral aldosterone-producing adenomas; NA, not applicable; UniAPA, unilateral aldosterone-producing adenomas. [a]An ARR >30 ng/dl per ng/ml/h with a PAC >10 ng/dl after administration of captopril was defined as a positive test. [b]A strict ARR was defined as an ARR >100 ng/dl per ng/ml/h and a PAC >20 ng/dl.[13] [c]A positive postural test was defined as an ambulatory PAC 30% greater than that of the supine baseline level.[3,19] *The ARR examination and image study were within 6 months before the first operation.

after the administration of 50 mg captopril (Table 3) ($p = 0.023$), in spite of a similar ratio before captopril administration (1044 ± 764 vs. 475 ± 308 ng/dl per ng/ml/h, $p = 0.101$). However, post-captopril ARR was not significant different between BiAPA and UniAPA patients ($p = 0.351$) (Table 3), or between UniAPA and BAH patients ($p = 0.218$) (Figure 4). BiAPA and UniAPA had the same baseline ARR ($p = 0.116$), the post-captopril ARR ($p = 0.351$) and rate of positive postural test ($p = 0.999$) (Table 3).

Using a strict cut-off level for ARR of >100 ng/dl per ng/ml/h and for PAC of >20 ng/dL, there was a significant difference between BiAPA and BAH patients ($p = 0.016$; Table 2). BiAPA also had a borderline significance of higher positive strict cut-off level for ARR after captopril than UniAPA ($p = 0.075$). The detection of aldosteronism by the strict post-captopril ARR (>100 ng/dl per ng/ml/h) yielded a 100% sensitivity and 61.9% specificity for BiAPAs. The area under the curve was 0.789 ± 0.111, $p = 0.0091$ (with area = 0.5) (Figure 5).

Discussion

Although BiAPAs are reportedly rare and difficult to diagnose, we demonstrated seven cases with bilateral functioning adenomas in 164 patients with APA, a distribution of 4.3%. The present study is the largest series of bilateral functional adenomas so far published. BiAPAs in these patients were diagnosed simultaneously in four patients and sequentially in three patients. For those who were diagnosed with BiAPAs simultaneously, bilateral partial adrenalectomy resulted in a cure of hypertension and an inappropriate secretion of aldosterone. In spite of visualization of unilateral adrenal lesions, the patients sequentially diagnosed with BiAPAs had normal BP and serum potassium levels after their first surgical procedure. Nevertheless, a high ARR persisted. This observation may indicate that small functional nodules in the contralateral adrenal gland may be present when unilateral APA is diagnosed.

Currently, the pre-operative diagnosis of BiAPAs remains elusive, and is usually made by a pathologist post-operatively. Adrenal tumours are frequently found at autopsy or incidentally detected during abdominal morphological evaluation in patients without adrenal dysfunction.[25] Microscopic analysis of the resected adrenal gland in our patients demonstrated large, encapsulated nodules, while the residual adrenal tissue showed no evidence of hyperplasia in the outer portions of the zona fasiculata. These findings were completely different from those in BAH, in which there is hyperplasia of the zona glomerulosa and the outer portions of the zona fasciculate,[24] and also different from those of nodular hyperplasia, which is marked by cortical cells streamed into the outer rim of zona facsiculata, adrenal capsule or periadrenal fat.[5] Bilateral functioning adenomas are very rare.[6–10] Another possibility would be a patient with a APA in one adrenal and a non-hyperfunctioning tumour in the other.[26–28] Thus, an adrenal nodule may not be

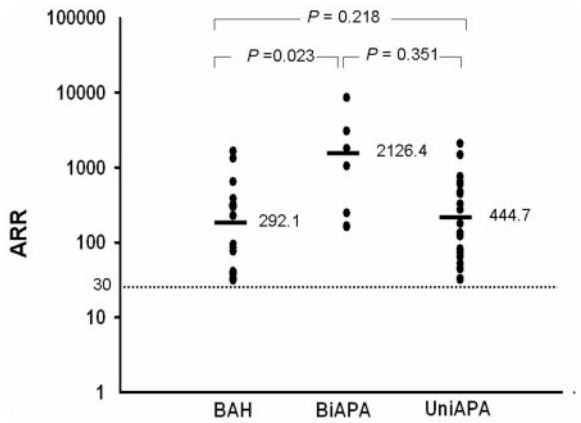

Figure 4. Comparison of the post-captopril aldosterone-to-renin ratio (ARR, ng/dl per ng/ml/h) of patients with bilateral aldosterone-producing adenomas to those with idiopathic bilateral adrenal hyperplasia and inilateral aldosterone-producing adenomas. All patients had an ARR >30. Black bars represent mean values.

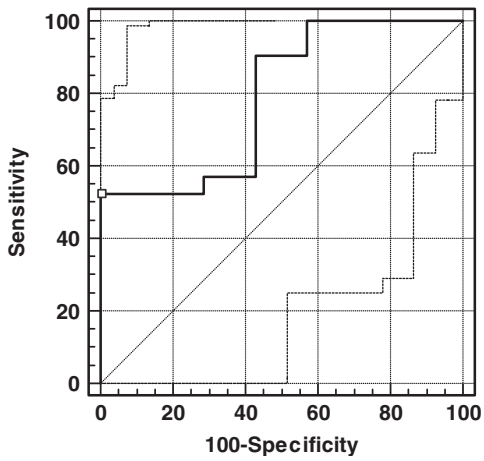

Figure 5. Receiver operating characteristic curves (ROC) to distinguish bilateral aldosterone-producing adenomas from idiopathic bilateral adrenal hyperplasia using the post-captopril aldosterone-to-renin ratio (ARR). The area under the curve = 0. 789 ± 0.111, $p = 0.0091$ (Area = 0.5). □, Cut-off (ARR = 100 ng/dl per ng/ml/h) with highest accuracy (sensitivity 100%, specificity 61.9%).

causative *per se* of aldosterone hypersecretion, and pre-operative identification of the functioning tumour should be performed.

Refinement of imaging techniques has facilitated the detection of subtle adrenal abnormalities early in the clinical course. Several diagnostic methods have been introduced to determine whether an adrenal mass is functional or non-functional. Yamamoto *et al*.[7] published the first case report of BiAPAs with bilateral uptake in the adrenal glands by DSS and AVS. In this regard, adrenocortical scintigraphy is a valid evaluation tool for primary aldosteronism especially for adrenal nodules.[29] However, a DSS scan has limitations in detecting small APAs.[30,31] In the present report, uptake of the radiotracer by both adrenal glands was observed in those who were diagnosed simultaneously with bilateral adenomas. Although one patient with a sequentially diagnosed APA had bilateral uptake of radiotracer, adrenal venous sampling suggested a unilateral adrenal lesion. Indeed, determination of the anatomic cause of PA remains problematic, because of the limited accuracy of CT scans, NP59 scans, and MRI imaging modalities. Even adrenal vein sampling, the gold standard of differential diagnosis of the subtypes of PA, has its limitations, because bilateral functional adenomas may or may not present at the same time. Although CT scanning cannot reliably discriminate BAH from APA,[22] in the current study and other previous reports, the finding of bilateral single focal macroadenomas on CT scan had a high positive predictive value when the tumour size was >1 cm.[30,31]

The present data need to be confirmed prospectively in a larger population. However, as n in other studies,[4,22,32] our data show that patients with BiAPAs have lower serum potassium levels, lower PRA and higher PAC than patients with BAH, but a similar ARR. Nevertheless, one study suggested that the basal ARR could differentiate unilateral APA from BAH.[33] Upright posture reportedly decreases PAC in APA, but raises PAC in BAH.[3,11,16,34] Our patients with BiAPAs showed a lower rate of a positive postural change than previously reported (14.3% vs. 21–65% with UniAPA,[3,16,34] similar to 23.8% in our UniAPA patients, Table 3). Although the positive rate of the postural change test was higher in BAH in the current study, it is unclear whether this test can clearly distinguish between APA and BAH,[3,11] and the observed difference may be due to an occasional angiotensin-responsive APA.[32] In our patients, only half of those with BAH had a positive postural change test. In this study, it was difficulty to subclass BiAPAs and UniAPAs except by imaging studies. The comparison between unilateral and bilateral APA would also be clinically relevant, as one challenge is to separate them from patients with APA in one adrenal and a non-hyperfunctioning tumour in the other.

The captopril test has been proposed as a simple tool for establishing a specific diagnosis of PA, and appears as efficacious as sodium loading in confirming a diagnosis of PA.[35–38] However, the diagnostic value of the captopril test in differentiating APA from BAH has not been elucidated.[11,32,34,38] A higher post-captopril ARR was noted in our patients with BiAPA than in those with BAH,[11,32] but was not significantly different between UniAPA and BAH. The post-captopril ARR may be dependent on the responsiveness of aldosterone to angiotensin-II. Therefore, the differentiation of APA from BAH may depend upon a portion of the angiotensin-II responsive subtype of APA patients. We did not examine the subtype of angiotensin-responsiveness in patients with BiAPAs. Post-captopril ARR >100 had a sensitivity of 100% in distinguishing APA from BAH, but at the cost of a low specificity (61.9%), and cannot be considered a good positive screening test for the diagnosis of BiAPAs in bilateral aldosteronism. A strict ARR is an effective negative screening tool, in that a low value reliably excludes BiAPA in patients with bilateral aldosteronism. A strict ARR >100 was previously determined to provide maximum specificity and sensitivity in identifying PA, and can separate APA from BAH.[13] Patients with bilateral adrenal lesions require careful evaluation of the possibility of BiAPAs if their post-captopril ARR is >100 ng/dl per ng/ml/h and the PAC is >20 ng/dl.

In conclusion, bilateral hyperfunctioning aldosteroma may not be rare, and may be diagnosed simultaneously or sequentially. The differentiation of this entity from BAH may not be clearly established using current diagnostic tools. Patients with bilateral functional aldosteronism presenting with an ARR >100 ng/dl per ng/ml/h after the captopril test should be carefully evaluated and followed for bilateral aldosteronism.

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