Original Article

Clinical Characteristics of Aldosterone-Producing Microadenoma, Macroadenoma, and Idiopathic Hyperaldosteronism in 93 Patients with Primary Aldosteronism

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Primary aldosteronism (PA) due to aldosterone-producing adenoma (APA) is a form of surgically curable secondary hypertension, and distinguishing APA from idiopathic hyperaldosteronism (IHA) is important for treatment. We made a differential diagnosis between APA and IHA using imaging tests such as adrenal CT and MRI as well as adrenal venous sampling (AVS) in all 93 cases of PA presenting at our institutions over the last decade. We identified 27 patients with aldosterone-producing microadenoma (APmicroA), all of whom could be diagnosed by AVS but not by the imaging tests. Then, we compared the clinical and roentgenological findings of these 27 patients with those of 42 patients with aldosterone-producing macroadenoma (APmacroA) and of 24 patients with IHA. Using surgically removed adrenal tissues, histopathological examinations and immunohistochemical analyses of steroidogenic enzymes were conducted. The findings for APmicroA were similar to those for APmacroA, except with respect to the diameter of the adrenal adenomas. Endocrinological and roentgenological findings for APmicroA were similar to those for IHA, but not to those for APmacroA. The rate of cure of hypertension was much greater in patients with APmicroA than in patients with APmacroA after the unilateral adrenalectomy (odds ratio, 4.0; $p=0.028$). In conclusion, it is important to accurately diagnose APmicroA, in which the laterality of the hyperproduction of aldosterone is only detectable by AVS, and to treat these patients by unilateral adrenalectomy in order to avoid long-term medical treatment and prevent hypertensive vascular complications. (*Hypertens Res* 2006; 29: 883–889)

***Key Words*: hyperaldosteronism, microadenoma, macroadenoma, hyperplasia, adrenalectomy**

Introduction

Primary aldosteronism (PA) is a curable form of secondary hypertension, and the incidence of PA among hypertensives is higher than previously reported (*1–6*). PA is endocrinologically and pathophysiologically classified as a form of aldosterone-producing adenoma (APA) (*7*), idiopathic hyperaldosteronism (IHA) (*8*), unilateral adrenal hyperplasia (UAH) (*9*), primary adrenal hyperplasia (*10*), adrenal cancer (*11*), glucocorticoid remediable aldosteronism (*12*), familial hyperaldosteronism type II (*13*) or unilateral multiple adrenocortical micronodules (UMN) (*14*). The most common types of PA are APA and IHA. APA typically responds to unilateral adrenalectomy, which corrects hyperaldosteronemia and can attenuate hypertension. The medical management of IHA is generally recommended (*15–18*), since unilateral or subtotal adrenalectomy results in only a 15–20% hypertension cure

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Received December 21, 2005; Accepted in revised form July 28, 2006.

rate (*10*, *15*). Therefore, distinguishing APA from IHA is critical for deciding on the type of treatment.

This can be achieved by using imaging tests such as CT, MRI and ^{131}I-labeled cholesterol adrenal scintigraphy. Doppman and Gill reported a method for detecting adrenal nodules by using thin-section cross-sectional imaging, and postulated the existence of APAs too small to be detected with imaging tests such as thin-section CT or MRI in the adrenals of patients with PA (*19*). Moreover, Young *et al*. reported a small APA of 6 mm in diameter (*20*). We also reported that 45 patients were diagnosed with APAs among 1,020 hypertensives who visited a general outpatient clinic (*21*), and 22 (49%) of these cases were detected by pathological examinations rather than by regular imaging methods such as enhanced thin-slice CT and MRI, because the APAs were less than 6 mm in diameter. Therefore, we compared the clinical, endocrinological, roentgenological, and pathological characteristics of aldosterone-producing microadenomas (APmicroAs), which can only be diagnosed by adrenocorticotropic hormone–stimulated adrenal venous sampling (ACTH-AVS), with those of aldosterone-producing macroadenomas (APmacroAs), which are readily detectable using each imaging test, and also with those of IHA showing bilateral adrenal hypersecretion of aldosterone in ACTH-AVS.

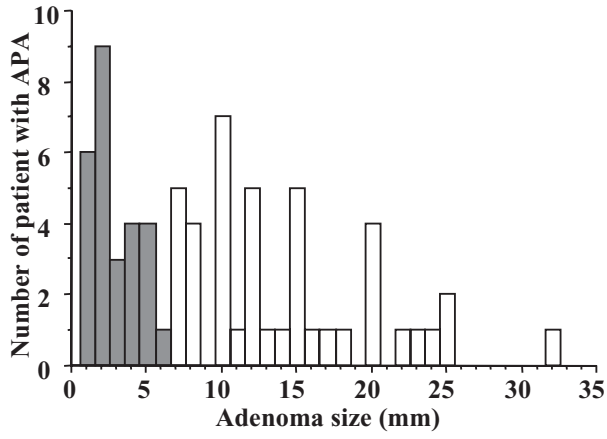

Fig. 1. *Distribution of the size of aldosterone-producing adenomas (APAs). The APAs varied widely in size from 1 to 32 mm in diameter. The shaded bar represents the number of aldosterone-producing microadenomas ≤6 mm in diameter that could only be diagnosed by ACTH-stimulated adrenal venous sampling. The open column represents the number of aldosterone-producing macroadenoma ≥7 mm in diameter that could be detected by imaging methods such as CT and MRI.*

Methods

Patients

The clinical records of 93 patients with PA were retrospectively analyzed. Seventy-two of the patients were diagnosed with PA after a screening of hypertensives visiting general outpatient clinics between 1995 and 2005 at Yokohama Rosai Hospital and Social Insurance Central General Hospital, while 21 were referred to these hospitals for further investigation of PA. The diagnosis was confirmed by endocrinological examinations such as the furosemide plus upright test and captopril-loading test (*22*), and ACTH-AVS. Sixty-nine patients were diagnosed with APA and underwent unilateral adrenalectomy. In all of these patients, hypersecretion of aldosterone from one of the adrenal glands was confirmed by ACTH-AVS, and the diagnosis of APA was confirmed by pathological examinations, including immunohistochemical examinations of steroidogenic enzymes as previously described (*14*). Twenty-four patients were suspected of having IHA, based on confirmation of the hypersecretion of aldosterone from both adrenal glands by ACTH-AVS. Two of these 24 patients were also treated by unilateral adrenalectomy, and the two resected adrenal glands were pathologically diagnosed with hypertrophy of the zona glomerulosa.

Measurements of Plasma Aldosterone Concentrations, Plasma Renin Activity, and Serum Cortisol Concentrations

None of the patients were taking any antihypertensive drugs at the time of blood sampling. Blood samples were collected in the morning after the patients had rested supine for 30 min. The plasma aldosterone concentration (PAC), the serum cortisol concentration, and the plasma renin activity (PRA) were each measured with a specific radioimmunoassay as reported previously (*14*). Patients with a PRA ≤1.0 ng/ml/h and a PAC ≥12.0 ng/dl were diagnosed as having hyporeninemic hyperaldosteronemia (*21*).

Furosemide plus Upright Test

Patients with hyporeninemic hyperaldosteronemia underwent a furosemide plus upright test in the morning after resting for at least 30 min supine as previously reported (*14*). PRA 120 min after the intravenous injection of 40 mg of furosemide and the maintenance of upright posture ($PRA_{furosemide}$) was measured. Patients with a $PRA_{furosemide}$ ≤1.0 ng/ml/h were diagnosed as probable cases of PA (*21*).

Captopril-Loading Test

Patients with hyporeninemic hyperaldosteronemia also received a captopril-loading test. PAC and PRA were measured 90 min after the oral administration of 50 mg of capto-

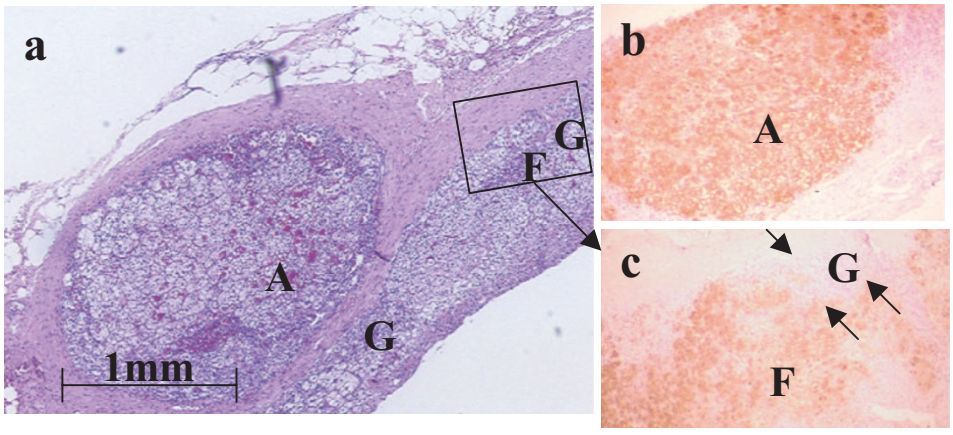

Fig. 2. *a: Histopathological features of aldosterone-producing microadenoma. A well-encapsulated adrenocortical adenoma of 2 mm (A) in diameter was observed in the resected right adrenal gland. Hematoxylin-eosin staining. b: Immunohistochemistry to 3β-HSD in the aldosterone-producing microadenoma. Immunoreactivity to 3β-HSD was detected in the cortical microadenoma cells. c: Immunohistochemistry to 3β-HSD in the non-nodular adrenal cortex. The zona glomerulosa of the non-nodular adrenal cortex showed hyperplasia. Immunoreactivity to 3β-HSD was detected in the zona fasciculata (F), but not in the hyperplastic zona glomerulosa (G). Arrows indicate the area of the zona glomerulosa.*

pril, and the ratio of PAC to PRA ($ARR_{captopril}$) was calculated. The patients remained supine during the test. Patients with an $ARR_{captopril} \geq 20$ ng/dl per ng/ml/h were diagnosed as probable cases of PA (*22*).

Adrenal Computed Tomography

Thin-section high-resolution CT scans of adrenal glands were performed in all patients with hyporeninemic hyperaldosteronemia. We obtained thin-section scans with a 2-mm collimation at 2-mm intervals after the intravenous injection of the contrast medium. The presence of nodules and hyperplasia in the adrenal glands examined by CT was diagnosed by two experienced radiologists.

Adrenocorticotropic Hormone–Stimulated Adrenal Venous Sampling

ACTH-AVS was performed in all patients diagnosed with probable PA to detect the side on which the hypersecretion of aldosterone occurred. Adrenal venous blood was selectively sampled before and 30 min after the intravenous injection of 250 μg of a synthetic adrenocorticotropic hormone (ACTH) (1–24) *via* the median cubital vein. The placement of the catheter tip at the adrenal vein was confirmed as previously reported (*21*). Furthermore, we judged that the catheters had been correctly inserted into the adrenal vein when cortisol levels in the adrenal venous effluents were more than 40 μg/dl before ACTH treatment and more than 200 μg/dl 30 min after the stimulation. We then made a diagnosis of aldosterone hypersecretion when the aldosterone concentrations in the adrenal venous effluents were more than 250 ng/dl before ACTH treatment and more than 1,400 ng/dl 30 min after.

Pathological Examinations

Tumor size was measured directly based on the gross pathology of the adrenals resected from the patients with APA. Histopathological and immunohistochemical analyses of steroidogenic enzymes, including cholesterol side chain cleavage enzyme ($P\text{-}450_{scc}$), 3β-hydroxysteroid dehydrogenase (3β-HSD), 21-hydroxylase ($P\text{-}450_{C21}$), 17-hydroxylase ($P\text{-}450_{C17}$), and 11β-hydroxylase ($P\text{-}450_{C11}$), were performed to differentiate small aldosteronomas with the paradoxical hyperplasia of the zona glomerulosa from IHA (*23*) on routinely processed formalin-fixed paraffin-embedded specimens by employing the biotin-streptavidin amplified method.

Statistical Analysis

The results are expressed as means±SD. Comparisons between two groups were performed with Student's *t*-test and the comparison of proportions was carried out using the χ^2 test. The level of significance was set at $p<0.05$.

Results

Histopathological examinations of the 69 resected adrenals revealed that the APAs varied widely in size from 1 to 32 mm in diameter (Fig. 1), and that the adrenal glands with APAs of less than 6 mm in diameter showed no abnormal findings on the high-resolution CT. We then divided APAs into two subtypes: APmacroAs (≥7 mm in diameter) and APmicroAs (≤6 mm in diameter) (Fig. 2a).

Table 1. Clinical Data of Patients with APmacroA, APmicroA and IHA

	APmacroA (n=42)	APmicroA (n=27)	IHA (n=24)
Age (years)	52.0±11.0	54.0±10.0	48.0±9.8**
Sex (male/female)	20/22	10/17	9/15
Systolic blood pressure (mmHg)	179±19	177±18	170±21
Diastolic blood pressure (mmHg)	101±11	101±13	99±14
Serum potassium (mEq/l)	3.3±0.7**	3.7±0.4	3.9±0.2‡‡
PAC (ng/dl)	26.2±14.7**	18.6±7.6	16.6±4.1‡‡
PRA (ng/ml/h)	0.3±0.3	0.4±0.3	0.5±0.4‡
ARR (ng/dl per ng/ml/h)	191±165**	89±85	65±53‡‡

Each parameter was determined as described in Methods. The parameters obtained from APmacroA, APmicroA and IHA were statistically calculated and the results are expressed as means±SD. Statistical analysis was performed with Student's t-test and the χ^2 test. APmacroA, aldosterone-producing macroadenoma; APmicroA, aldosterone-producing microadenoma; IHA, idiopathic hyperaldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone-renin ratio. **$p<0.01$ compared with APmicroA, ‡$p<0.05$ compared with APmacroA, ‡‡$p<0.01$ compared with APmacroA.

The data showed that 27 patients had APmicroA and 42 had APmacroA. An immunohistochemical analysis of steroidogenic enzymes was performed using the samples of resected adrenal glands obtained from 14 of 27 patients with APmicroA, all of whom underwent a unilateral adrenalectomy, from 10 of 42 patients with APmacroA who also received a unilateral adrenalectomy, and from 2 of 24 patients with IHA who underwent only a unilateral adrenalectomy. Immunohistochemical analysis demonstrated the immunoreactivity to P-450$_{scc}$, 3β-HSD (Fig. 2b), P-450$_{C21}$, P-450$_{C17}$ and P-450$_{C11}$ in cortical cells of APmicroA. The findings of the immunoreactivity in APmicroA were similar to those in APmacroA (data not shown). The immunoreactivity for 3β-HSD in the hyperplastic zona glomerulosa, which was positive in IHA, was negative in APmicroA (Fig. 2c) and APmacroA.

The clinical features of the 27 patients with APmicroA, 42 with APmacroA, and 24 with IHA are summarized in Table 1.

There was no difference in blood pressure among the patients with APmicroA, with APmacroA, and with IHA. Serum potassium levels were significantly higher in APmicroA than in APmacroA (p=0.01). PAC was significantly lower in APmicroA than in APmacroA (p=0.01). PRA in APmicroA was similar to that in APmacroA, while the PAC to PRA ratio (ARR) was significantly lower in APmicroA than in APmacroA (p=0.004). Serum potassium levels, PAC, PRA, and ARR in patients with APmicroA were similar to those in patients with IHA (Table 1).

As shown in Fig. 3a, the furosemide plus upright test revealed that PRA$_{furosemide}$ was significantly lower in patients with APmacroA than in patients with IHA, while there was no significant difference in PRA$_{furosemide}$ of APmicroA, compared with APmacroA and IHA. As shown in Fig. 3b, the captopril-loading test revealed that ARR$_{captopril}$ was significantly higher in patients with APmacroA than in patients with APmicroA or IHA, while ARR$_{captopril}$ in patients with APmicroA was similar to that in patients with IHA.

CT showed unilateral adrenal tumors in 35 patients and bilateral adrenal tumors in 4 of 42 patients with APmacroA, but it could not detect 3 APmacroAs with diameters of 7, 8, and 11 mm. Moreover, CT could not be used to clarify abnormalities in the adrenals of 22 of 27 patients with APmicroA, whereas in the other 5 patients, CT revealed adrenal tumors larger than 7 mm in diameter that were located on the side contralateral to the APmicroA. Five patients showing the presence of adrenal tumor ≥7 mm in diameter on the side opposite to the APmicroA were treated by unilateral adrenalectomy of the affected adrenal containing APmicroA. After the unilateral adrenalectomy, the hyporeninemic hyperaldosteronemia in these 5 patients improved and the blood pressure of 4 of the patients decreased to less than 140/90 mmHg.

One year after the unilateral adrenalectomy, PAC in the 69 patients with APA had returned to within the normal range, and the blood pressures of 22 (81%) of 27 patients with APmicroA and 22 (52%) of 42 patients with APmacroA had decreased to less than 140/90 mmHg without the administration of antihypertensive agents. Therefore, the rate of cure of hypertension after the unilateral adrenalectomy in patients with APmicroA was significantly better than that in patients with APmacroA (odds ratio, 4.0 [95% confidence interval, 1.3 to 12.6]; p=0.028).

Discussion

According to our findings, the incidence of APmicroA, APmacroA, and IHA among patients with PA was 29%, 45% and 26%, respectively. The clinical and roentgenological findings of APmicroA were similar to those of IHA rather than APmacroA, while the pathological findings of APmicroA were similar to those of APmacroA. Our data also demonstrated that the rate of cure of hypertension was higher in patients with APmicroA than in those with APmacroA after the unilateral resection of the affected adrenal gland in which

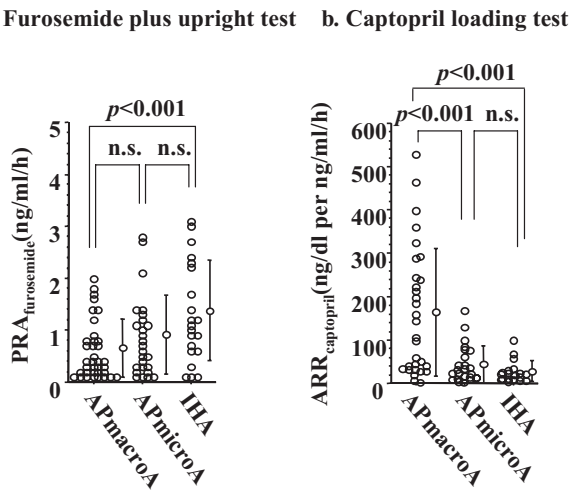

Fig. 3. *The results of the furosemide plus upright test and captopril-loading test. a: Plasma renin activity 120 min after the intravenous injection of 40 mg of furosemide and the maintenance of upright posture ($PRA_{furosemide}$) in patients with aldosterone-producing macroadenoma (APmacroA), aldosterone-producing microadenoma (APmicroA) and idiopathic hyperaldosteronism (IHA). b: Aldosterone-renin activity ratio 90 min after the oral administration of 50 mg of captopril ($ARR_{captopril}$) in patients with APmacroA, APmicroA, and IHA.*

the hypersecretion of aldosterone was confirmed by ACTH-AVS.

The prevalence of PA among hypertensives has increased along with the wider application of PAC and PRA measurements for the screening of PA (*24*, *25*). The proportion of APA and IHA has been reported to differ quite markedly according to the screening test used (*24*). The prevalence of IHA has recently been reported to be higher than that of APA in cases of PA (*3*, *4*, *24–28*). On the other hand, we had already reported a prospective study describing that the prevalence of APA was much higher than that of IHA after the screening for PA among 1,020 hypertensives visiting a general outpatient clinic (*21*). The present study clearly demonstrated that the prevalence of APA, which consisted of both APmicroA and APmacroA, and that of IHA were 74% and 26% among 93 patients with PA, respectively.

CT is a common and useful clinical tool for detecting adrenal masses and distinguishing APA from IHA (*29*, *30*). However, several studies have reported that adrenal CT imaging is not a reliable method for differentiating PA (*26*, *31*, *32*). In the present work, thin-section high-resolution CT could not delineate 27 cases of APmicroA among 69 cases of APA, because CT could not detect an adrenal mass ≤6 mm in diameter. Mulatero *et al*. suggested that the prevalence of IHA could be overestimated due to an over-reliance on the imaging findings of CT and the results of posture studies (*25*). Therefore, we might misdiagnose APmicroA as IHA if we attempt to distinguish APA from IHA based on the findings of imaging methods such as adrenal CT and MRI.

Adrenal venous sampling (AVS) is now thought to be the best method of detecting unilateral or bilateral lesions in the adrenals in PA in order to distinguish APA from IHA (*33*). Higher incidences of APA than IHA among cases of PA were recently observed in various countries where AVS or ACTH-AVS is usually performed for the differentiation of APA from IHA (*5*, *21*, *34*, *35*). Tiny lesions such as APmicroA, UAH (*9*) and UMN (*14*) have been diagnosed by ACTH-AVS. We have been performing ACTH-AVS since 1994 to distinguish between unilateral and bilateral hypersecretion of aldosterone, and we have been able to adequately diagnose APmicroAs, which are impossible to detect by CT, by this method.

Our data also showed that the diagnosis of PA due to APmicroA is critical because the rate of cure of hypertension after the unilateral adrenalectomy was better in patients with APmicroA than in patients with APmacroA. The rate of cure of hypertension after unilateral adrenalectomy in patients with PA due to aldosteronoma has been reported to range from 30% to 68% (*15*, *18*, *36–38*). Our data also revealed that hypertension was completely cured 1 year after the unilateral adrenalectomy in 22 of 27 patients with APmicroA (81%) and in 22 of 42 patients with APmacroA (52%). Thus, surgical treatment with the unilateral adrenalectomy is more promising for patients with APmicroA than for patients with APmacroA.

It has been reported that aldosterone plays a crucial role in the development of damaged organs following heart failure, fibrotic changes in blood vessels, and renal failure (*39–42*). Thus, it is very important to attenuate hyperaldosteronemia in patients with PA to prevent various aldosterone-induced complications, especially after differentiating APmicroA from IHA and treating patients with APmicroA by unilateral adrenalectomy.

In conclusion, the present study revealed that the incidence of APmicroA is unexpectedly high among patients with PA and that APmicroA can be simply treated by unilateral adrenalectomy. Thus, it is important to accurately diagnose APmicroA, in which the hyperproduction of aldosterone is only detectable by ACTH-AVS, and to treat these patients by unilateral adrenalectomy in order to avoid long-term medical treatment and prevent hypertensive vascular complications.

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