Guidelines for the diagnosis and treatment of primary aldosteronism — The Japan Endocrine Society 2009 —

Tetsuo Nishikawa¹⁾, Masao Omura²⁾, Fumitoshi Satoh³⁾, Hirotaka Shibata⁴⁾, Katsutoshi Takahashi⁵⁾, Naohisa Tamura⁶⁾ and Akiyo Tanabe⁷⁾; The Task Force Committee on Primary Aldosteronism, The Japan Endocrine Society

¹⁾ Department of Medicine, Yokohama Rosai Hospital, Yokohama, Japan

²⁾ Endocrinology & Diabetes Center, Yokohama Rosai Hospital, Yokohama, Japan

³⁾ Division of Nephrology, Endocrinology and Vascular Medicine, Tohoku University Hospital, Sendai, Japan

⁴⁾ Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan

⁵⁾ Department of Nephrology and Endocrinology, University of Tokyo, Graduate School of Medicine, Tokyo, Japan

⁶⁾ Department of Endocrinology and Diabetes, Koseikai Takeda Hospital, Kyoto, Japan

⁷⁾ Department of Medicine, Institute of Clinical Endocrinology and Hypertension, Tokyo Women's Medical University, Tokyo, Japan

Abstract. The Japan Endocrine Society (JES) attempted to develop guidelines for the diagnosis and treatment of primary aldosteronism (PA). The Task Force Committee (TFC) was composed of a chair, selected by the JES, and additional experts. Systematic reviews of available evidence for Japanese patients were used to recommend the key treatment and prevention. We have evaluated the methods of screening, confirmatory tests and imaging, plus adrenal vein sampling (AVS). Consensus was guided by systematic review of evidence and discussion during each annual meeting of the JES, plus its related meetings, and by e-mail communication. The drafts prepared by TFC were reviewed successively by the members of Research on Intractable Diseases provided by the Japanese Ministry of Health, Labour and Welfare, and in comments from the JES's councilors. At each stage of review, TFC received written comments and incorporated suggested changes. In conclusion, all patients with hypertension should be screened for PA, because of the high prevalence of cardiovascular disease and the current low case-detection rate in Japan. Case detection can be performed in hypertensive patients and those with hypokalemia by determining the aldosterone/renin ratio, and the diagnosis of PA can be confirmed by two of three confirmatory tests. The presence of a unilateral aldosterone-producing adenoma should be established/excluded by AVS by an experienced radiologist, optimally followed by laparoscopic adrenalectomy. In contrast, patients with bilateral adrenal hyperplasia, or those unsuitable for surgery, are optimally treated medically with mineralocorticoid receptor antagonists.

Key words: The Japan Endocrine Society, Guidelines, Primary aldosteronism, Hypertension, Adrenal vein sampling

I. Background

Primary hyperaldosteronism (PA) is caused by the autonomous secretion of aldosterone from adrenocortical lesions, and is associated with hypertension due to sodium (Na) retention, hypokalemia due to increased potassium (K) excretion, and organ disorders (cerebral hemorrhage, cerebral infarction, myocardial infarction,

cardiomegaly, arrhythmia, renal insufficiency, etc.) due to inappropriate aldosterone levels [1-3]. PA is usually caused either by aldosterone-producing adenoma (APA) in one adrenal or bilateral hyperplasia of the zone glomerulosa (idiopathic hyperaldosteronism: IHA), but it may also be caused by small hyperplastic lesions of one adrenal gland (unilateral adrenal hyperplasia (UAH), unilateral multiple adrenocortical nodules (UMN)), bilateral APAs, and hereditary glucocorticoid-remediable aldosteronism (GRA). Conn [4], who first reported PA due to an adrenal tumor, considered it to be common, representing 20% or more of all hypertensives. Subsequent studies, which conducted on the basis that hypokalemia was a required for diag-

Submitted Jul. 13, 2011; Accepted Jul. 19, 2011 as EJ11-0133

Released online in J-STAGE as advance publication Aug. 9, 2011

Correspondence to: Tetsuo Nishikawa, M.D., Ph.D., Department of Medicine, Yokohama Rosai Hospital, 3211 Kozukue-cho, Kohoku-ku, Yokohama City 222-0036, Japan.

E-mail: tetsuo@yokohamah.rosai.go.jp

nosis, suggested that it is rare, accounting for 1% or less of all hypertensives. In recent studies, however, the percentage of patients with hypokalemia, which was previously considered a characteristic symptom of this disease, is 9-37% in overseas studies [5], and 18% in Japan [6, 7], indicating that a diagnosis of PA requiring hypokalemia is misleading particularly in Japan. Moreover, recent screening of hypertensive patients in Japan using simultaneous measurement of the plasma aldosterone concentration (PAC) and plasma renin activity (PRA), or the aldosterone-renin ratio (ARR) has shown that PA is found in 3.3-10% of hypertensive patients and is the most frequent cause of secondary hypertension [5-10]. Therefore, it has become clear that PA may often be overlooked in hypertensive patients if hypokalemia is considered to be required for the diagnosis. With proper treatment based on an appropriate diagnosis, secondary hypertension can be cured, and organ disorders prevented, in patients with PA. However, since small APAs with a diameter of 6 mm or less, which cannot be detected by imaging examinations, account for about half of all APAs [11], some PA patients show a CT-detectable adrenal tumor that is not producing excess aldosterone and the contra-lateral adrenal micro-lesion causing hyperaldosteronism. Thus, it is difficult to definitely diagnose the laterality of hyperaldosteronism only by CT images. While dexamethasone-suppressed adrenal scintigraphy has also been used, its diagnostic accuracy is unsatisfactory. Therefore, in selecting cases for surgical treatment among patients with PA, blood sampling from the adrenal veins, which can accurately localize the source of the elevated aldosterone levels, should be performed to the extent that it is possible.

II. Outline of these guidelines

A characteristic of these guidelines is that they recommend more appropriate and efficient screening and definitive diagnosis by employing two individual guidelines, one for general practitioners who perform initial screening, which is crucial for detection of patients with PA, and the second for specialist medical facilities that perform expert diagnosis and treatment, including adrenal vein sampling.

The guidelines also recommend not only the captopril-challenge test but also saline loading, oral salt loading, and furosemide loading-upright posture tests for confirmation on exclusion of the diagnosis of PA.

They also describe the method for adrenal vein sampling, which is necessary for the selection of treatment for the disease, and diagnostic criteria based on evidence in Japanese patients.

III. Screening

1. Target patients

- 1) The guideline for general practitioners recommends measurement of the plasma renin activity (PRA) and plasma aldosterone concentration (PAC) in all patients initially diagnosed as hypertensive without strictly restricting blood sampling conditions to screen them for PA. It then recommends either immediate referral of patients possibly with PA or performing the captopril-challenge test, if possible, and the referral of those more likely to have the disease to specialist medical facilities (Fig. 1).
- 2) The guideline for specialist medical facilities is demonstrating that all hypertensive patients are intended to be applied for screening. The Guidelines for the Treatment of Hypertension 2009 (JSH 2009) [10] and the clinical practice guideline of the Endocrine Society [5] recommend the selective screening of high-risk groups for PA such as those with resistant (refractory) hypertension, grade II-III hypertension, and hypokalemia. However, since the proportion of PA is reported to be up to 10% among hypertensive patients [5-10], we recommend, at least at specialist medical facilities, to examine the PRA and PAC in all hypertensive patients with this disease in mind (Figs. 2-1, 2-2).

2. Screening method

The guidelines recommend screening of patients for PA by simultaneously measuring the PAC (pg/mL) and PRA (ng/mL/hr) and calculating the PAC/PRA ratio (ARR).

PA screening should be performed with the criterion of $ARR > 200$ on the basis of a report that the ARR is suitable [12]. However, as values of ARR may change with the context, for more accurate screening, its measurement should be repeated even if a normal value has been obtained on a single measurement [13] (Caution: The possibility of this disease increases if $ARR > 200$ and $PAC > 120-150$ pg/mL). If the patient is medicated, since many antihypertensive drugs affect the renin-angiotensin-aldosterone (RAA) system, it is recommended to measure the ARR after changing the anti-

hypertensive drugs according to the supplementary comments in Fig. 1 and Fig. 2-1 below.

3. Problems regarding the methods for aldosterone assay and assessment of the results

In these guidelines, values for aldosterone concentration are presented according to the instructions of the SPAC-S Aldosterone Kit. For diagnosis, if the aldosterone concentration has been determined with a kit other than SPAC-S, the value must be converted using a conversion equation. Also, as the aldosterone concentration is reported in pg/mL or ng/dL, attention to the units is necessary. In these guidelines, the aldosterone concentration is presented as pg/mL.

Notes:

(1) The relationship between the values obtained with the SPAC-S Aldosterone kit and Aldosterone RIA Kit II is as follows:

$$y = 7.67x - 6.7 \quad (r = 0.9662, n = 122)$$

y (pg/mL): SPAC-S Aldosterone kit (TFB, Inc.)

x (ng/dL): Aldosterone RIA Kit II (Dynabot)

(2) The absence of adequate standards for aldosterone causes variation in the results of assays between kits.

4. Effects of antihypertensive drugs on the PRA and PAC

1) Angiotensin II receptor blockers (ARB) and

angiotensin-converting enzyme (ACE) inhibitors increase the PRA and reduce the PAC, causing a decrease in the ARR (risk of false-negative results). Therefore, hyporeninemia ($PRA < 1.0$ ng/mL/hr) strongly suggests PA during the use of these drugs. Discontinuation of medication is often not necessary, but repeat assays must be performed, after the discontinuation of medication, if $PRA > 1.0$ ng/mL/hr.

2) Since β -blockers reduce the PRA more markedly than they reduce the PAC, they raise the ARR. Therefore, essential hypertension may be diagnosed as PA (risk of false-positive results). Screening after their withdrawal for 2 weeks or longer is desirable.

3) Ca channel blockers increase the PRA and cause no change or a decrease in the PAC, leading to a decrease in the ARR. Therefore, mild PA may be judged to be essential hypertension (risk of false-negative results).

4) Diuretics and mineralocorticoid receptor (MR) antagonists increase the PRA and PAC, but as the increase in the PRA surpasses that in the PAC, they reduce the ARR (risk of false-negative results). Since diuretics and MR antagonists have the most marked effects on the ARR, patients using these drugs should be screened after their withdrawal for 6 weeks or longer.

Fig. 1 Diagnostic procedures for primary aldosteronism (for general practitioners)

Numerical numbers with asterisks indicate each explanation in detail, as described in the supplementary comments in the Text.

Supplementary comments for Fig. 1 (*1-4)
(for general practitioners)

*1: Blood may be sampled in the sitting position, but, if possible, it is better to sample blood after 30-minute bed rest.

- 1) PAC: Plasma aldosterone concentration (pg/mL)
(Pay attention to the unit: 10 times values in ng/dL are values in pg/mL)
- 2) PRA: Plasma renin activity (ng/mL/hr)

*2: In patients using diuretics, MR antagonists or β -blockers, the PAC/PRA ratio should be determined after changing these drugs to other antihypertensive drugs while monitoring the blood pressure (Diuretics and MR antagonists should be withdrawn 6 weeks or longer, and β -blockers 2 weeks or longer, before measurement).

Other antihypertensive drugs include:

- 1) Budralazine (Buterazine[®])
- 2) α -blockers: Doxazosin (Cardenal[®]), etc.
- 3) Ca channel blockers: Manidipine (Calslot[®]), controlled-release nifedipine (Adalat CR[®]), amlodipine

(Amlodin[®], Norvasc[®]), etc.

However, these drugs also affect the RAA system. It has been reported that Ca blockers may suppress the synthesis or action of aldosterone, possibly making the diagnosis of PA difficult.

(The above 3 classes of drug may be used in combination in patients with poorly controlled hypertension, with the exception of diuretics, MR antagonists, and β -blockers.)

*3: Educational facilities for post-graduate residency developed by the Japan Endocrine Society are recommended.

*4: Captopril-challenge test

- 1) Administration of 50mg captopril (four crushed 12.5-mg captopril (Captoril[®]) tablets, crushed)
- 2) Sampling of blood after 60 (90)-minute bed rest (or rest in the sitting position)
- 3) Evaluation: Judged to be positive with a PAC/PRA ratio >200 (or a PAC>120 pg/mL) after administration.

Fig.2-1 Diagnostic procedures for primary aldosteronism (for specialist medical facilities, screening and confirmation tests)
Numerical numbers with asterisks indicate each explanation in detail, as described in the supplementary comments in the Text.

**Supplementary comments for Fig. 2-1 (*1-9)
(for specialist medical facilities)**

*1: The screening procedure shown here is performed as a measure to exclude secondary hypertension such as renal parenchymal hypertension, renovascular hypertension, endocrine hypertension, aortic coarctation, brainstem vessel compression, sleep apnea syndrome, and drug-induced hypertension.

*2: The drugs are changed to those shown in 3 depending on the severity of hypertension, with the PAC/PRA ratio (ARR) then determined (The use of diuretics and MR antagonists must be discontinued for 6 weeks or more, and that of β -blockers for 2 weeks or more, before measurement).

*3: The following drugs can be used for treatment.

- 1) Budralazine
- 2) α -blockers: Doxazosin, etc.
- 3) Ca antagonists: Manidipine, controlled-release nifedipine, amlodipine, etc.

*4: If control of the blood pressure is unsatisfactory with the 3 classes of drug shown in 3, the addition of ARBs or ACE inhibitors should also be considered.

*5: Blood sampling may be performed after 15-minute rest in the sitting position (although 30-minute bed rest is recommended as far as possible).

1) PAC: Plasma aldosterone concentration (pg/mL)

2) PRA: Plasma renin activity (ng/mL/hr)

*6: Blood sampling in the morning is recommended, as the PAC is known to decrease in the afternoon. Careful evaluation is necessary when the PAC/PRA ratio (ARR) is less than 200, if a patient with refractory hypertension is screened during the use of multiple antihypertensive drugs and the blood is sampled in the afternoon (In patients with resistant (refractory) hypertension with a recent exacerbation and an ARR less than 200 on afternoon blood sampling, a repeat measurement of the ARR in the morning should be done).

*7: Since the PRA decreases so that the ARR increases

Fig. 2-2 Localization of adrenal masses and treatment. (for specialist medical facilities)

Numerical numbers with asterisks indicate each explanation in detail, as described in the supplementary comments in the Text.

in elderly people, false-positive results are occasionally observed. The specificity can be improved by the concomitant evaluation of the absolute value of the PAC (>120-150 pg/mL). At the same time, attention to the risk of overlooking early PA is necessary.

In addition, since PRA may vary widely from low to high in patients with renal disorders, renal failure, or during dialysis, judgment may thus be difficult.

*8: Evaluation is possible even during the use of ARBs or ACE inhibitors in patients with severe hypertension (with marked aldosterone secretion).

*9: If active renin concentration (ARC: pg/mL) is used instead of PRA, a PAC/ARC ratio >40 should be used as the criterion. The use of the ARC is advantageous in that the blood samples for the measurement of the PAC and ARC can both be stored at room temperature. Note that cooling with ice increases the ARC due to cryoactivation.

IV. Methods for a definitive diagnosis

If the ARR is high, it is recommended to make a definitive diagnosis by performing at least 2 of 3 confirmation tests (captopril-challenge test, upright furosemide-loading test, and saline-loading test) before attempting localization by adrenal vein sampling (Fig. 2-1). These tests are performed at a specialist medical facility, in principle.

*Supplementary comments for Fig. 2-1 (*10-16) (for specialist medical facilities)*

*10: The following examinations should be performed after correction of hypokalemia. Given salt intake restriction is indicated, according to the JSH2009, the possibility of a decrease in the ARR associated with an increase in the PRA should be considered when evaluating the results of each test.

Captopril-challenge test

*11: Attention to shock associated with a captopril-induced excessive decrease in the blood pressure is necessary in patients with angioedema or renovascular hypertension.

*12: Captopril-challenge test

- 1) Blood sampling after 30-minute bed rest (or rest in the sitting position).

- 2) Administration of four 12.5-mg captopril tablets, crushed (=50 mg).
- 3) Blood sampling after 60 (90)-minute bed rest (or rest in the sitting position).
- 4) Judgment criterion: PAC/PRA ratio >200 (or PAC/ARC ratio >40) (or PAC >120 pg/mL) after administration

Upright furosemide-loading test

*13: This test must be avoided in patients with advanced atherosclerosis at high risk for cerebrovascular events, and in those in whom arrhythmia may be induced by the test.

*14: Upright furosemide-loading test

- 1) Blood sampling after 30-minute bed rest
- 2) Intravenous injection of 40 mg furosemide
- 3) Two-hour standing (walking is permitted) followed by blood sampling in the sitting position
- 4) Judgment criterion: PRA <2.0 ng/mL/hr after loading (or ARC <8.0 pg/mL after loading)

Saline-loading test

*15: This test must be avoided in patients with reduced cardiac function and those suspected of having heart failure.

*16: Saline-loading test: It is desirable to perform the test under inpatient observation.

- 1) Blood sampling after 30-minute bed rest
- 2) Intravenous infusion of 2 L of saline over 4 hours (Ex.: From 8:00 to 12:00)
- 3) Blood sampling during bed rest after 4 hours (ambulation for urination is permitted after pre-loading blood sampling until 30 minutes before post-loading blood sampling).
- 4) Judgment criterion: Post-loading PAC >60 pg/mL (>8.5 ng/dL with Dynabot RIA Kit II). It is well known that changes in aldosterone during saline-loading test are usually observed because of diurnal rhythm of ACTH. It is sometimes useful to simultaneously determine cortisol for judging the results.
- 5) During the test, the blood pressure and symptoms must be monitored, with safety the first consideration
- 6) If renin suppression after loading is insufficient, attention to the possibility of secondary aldosteronism is appropriate.

Notes:

(1) If the saline-loading test is difficult to perform, a definitive diagnosis is also possible by the oral salt-loading test, which can be performed on an outpatient basis. However, it is desirable to perform even the oral salt-loading test on an inpatient basis if the patient has severe heart failure or serious arrhythmia.

(2) Oral salt-loading test

(i) On an inpatient basis, the patient is given a 12-g/day salt diet for 3 days, and 24-hour urine pooling is performed thereafter (If a 12-g/day salt diet is unavailable at the hospital, the salt intake is adjusted by prescribing additional salt). The 24-hour urinary aldosterone and Na excretion is determined, and PA is definitively diagnosed if the urinary aldosterone excretion is $>8\mu\text{g/day}$ ($\text{Na}>170\text{mEq/day}$) (Criterion at Mayo Clinic: Urinary aldosterone excretion $>12\mu\text{g/day}$ ($\text{Na}>200\text{mEq/day}$)).

(ii) On an outpatient basis, 24-hour urine pooling is performed during free dietary intake without salt-loading, and PA can be definitively diagnosed if the urinary aldosterone excretion is $>8\mu\text{g/day}$ with a urinary Na excretion $>170\text{mEq/day}$. If the urinary Na excretion is $<170\text{mEq/day}$, aldosterone suppression is insufficient. Under this condition, however, PA is considered unlikely if the urinary aldosterone excretion is $<8\mu\text{g/day}$, and the diagnosis needs to be confirmed if it is $>8\mu\text{g/day}$.

V. Subtype diagnosis (Disease typing)

In patients diagnosed with PA abdominal CT should be performed. If an adrenal mass is confirmed, it may be a non-functional adrenal adenoma, pheochromocytoma, cortisol-producing adenoma of Cushing's syndrome or subclinical Cushing's syndrome, or adrenal cancer (Fig. 2-2). If the patient can physically tolerate and wishes to undergo surgical treatment for PA, adrenal vein sampling (AVS) is necessary to determine whether aldosterone hypersecretion is bilateral or unilateral, and, if unilateral, which adrenal gland is responsible [11, 14].

**Supplementary comments for Fig. 2-2 (*17-21)
(for specialist medical facilities)**

*17: Cooperation with facilities capable of AVS must be considered.

Imaging studies***18: Imaging studies**

1) CT scanning: CT should be performed in consideration of the following points:

(1) CT should not be performed as a stand-alone diagnostic for PA lateralization [11, 14, 15], i.e., searching for the responsible lesion by CT alone should be avoided.

(2) The success rate of AVS can be improved by identifying the adrenal vein using contrast-enhanced MDCT.

(3) If an adrenal tumor 2 cm or greater in diameter is detected, the possibility of non-functional adrenal tumor, subclinical Cushing's syndrome or adrenal cancer must be considered.

(4) Exclusion of pheochromocytoma

2) Dexamethasone-suppression ^{131}I -adosterol scintigraphy: This examination should be performed when necessary in consideration of the following:

(1) The ability of ^{131}I -adosterol scintigraphy to determine the site of the lesion responsible for PA is very low [16]. If it is performed to search for the lesion responsible for the disease, the synthesis of endogenous cortisol and adrenal androgen must be suppressed by the oral administration of dexamethasone.

(2) ^{131}I -Adosterol scintigraphy without dexamethasone suppression is useful for the judgment of whether PA is complicated by cortisol-producing adenoma (in subclinical Cushing's syndrome, etc.).

Adrenal vein sampling (AVS)

*19: AVS is not performed in patients who do not wish to undergo surgical treatment. (There has been no randomized comparative study comparing the long-term prognosis between drug and surgical treatments for aldosterone-producing adenoma. However, according to the national epidemiological study of adrenal hormone production abnormalities performed from 1992 to 1996 by the Study Group on Adrenal Hormone Production Abnormalities, a Disease Specified by the Ministry of Health, Labour and Welfare, the improvement rates of hypertension and hypokalemia in patients with unilateral aldosterone-producing adenomas were slightly better in the group treated surgically than in the group treated with drugs alone) [17].

***20: Adrenal vein sampling (AVS)**

1) Objectives of AVS

AVS is performed in patients with PA to determine

whether the sites of aldosterone hypersecretion are bilateral or unilateral, and, if unilateral, which adrenal gland is responsible, and to evaluate indications for surgery.

2) Indications for AVS

AVS should be offered to patients who have been diagnosed with PA based on confirmatory tests and wish to be treated surgically if there are appropriate indications.

3) Methods for AVS

(1) Among antihypertensive drugs for blood pressure control, budralazine and α -blockers can be used until immediately before AVS, but other drugs may affect adrenal aldosterone secretion. If control of the blood pressure is insufficient with budralazine and α -blockers, the use of Ca channel blockers should be considered. Diuretics or MR antagonists should not be used (because they cause an increase in the adrenal venous PAC associated with an increase in the PRA even in the normal adrenal gland, possibly causing false-positive results). If an ACE inhibitor or ARB is administered before AVS, attention to a possible change in the evaluation criteria is necessary.

(2) If AVS is performed after dexamethasone-suppression adosterol adrenal scintigraphy, it should be performed 3 weeks or longer after the end of the dexamethasone administration (because cortisol secretion is suppressed, possibly affecting 21-1, the "judgment of adrenal vein catheterization").

(3) An IV line using a 3-way stopper is secured in a left elbow vein.

(4) A sheath is inserted into the right femoral vein employing the Seldinger method. (Two sheaths are used for simultaneous bilateral sampling.)

(5) A guide wire is advanced to the left femoral vein, a catheter for the left adrenal gland is advanced from the left femoral vein to the left external iliac vein, and the structure of catheter is modified, according to the 3D structure of the venous stream detected by CT.

(6) The catheter is advanced from the left renal vein to the left adrenal vein, contrast-enhancement is performed with a small amount of contrast medium, and the left inferior phrenic vein, left adrenal central vein and its lateral branches, and left renocapsular veins are identified (Fig. 3, right). The tip of the catheter is inserted precisely into the left adrenal central vein distally to the division of the left inferior phrenic vein and proximally to the division of

the lateral branch of the left adrenal vein, and blood is sampled. For this purpose, microcatheters are often necessary. After sampling, the position of the catheter tip is confirmed again by injecting a small amount of the contrast medium.

(7) Femoral venous blood or peripheral blood (or blood from the inferior vena cava at a point distal to the renal vein) is sampled.

(8) A catheter for the right adrenal gland is inserted into the right adrenal vein. After locating the right adrenal vein using a small amount of contrast medium, blood is sampled, and the position of the catheter tip confirmed using a small amount of contrast medium (Fig. 3, left).

(9) While leaving the catheter in the right adrenal vein, 0.25 mg of synthetic ACTH (tetracosactide acetate: Cortrosyn[®]) is administered through the 3-way stopper of the line in the elbow vein to improve diagnostic accuracy. Blood is sampled within 15 to 45 minutes after stimulation with ACTH from the right adrenal vein, femoral or peripheral vein (or inferior vena cava distal to the renal vein), and left adrenal vein.

(10) After withdrawal of the catheter, compression hemostasis of the puncture site is performed. Following treatment for the prevention of venous thrombosis, the patient is rested in bed for 1 hour, and released after confirming hemostasis of the puncture site.

Note:

It is desirable to perform ACTH stimulation to improve the diagnostic accuracy. If simultaneous bilateral sampling is performed, the catheter for the left adrenal vein must also be kept in the left adrenal vein after sampling until the end of blood sampling with ACTH-loading.

*21: Evaluation criteria for AVS.

1) Criteria for adequate catheterization in AVS

(1) An adrenal venous cortisol concentration after ACTH stimulation ≥ 200 $\mu\text{g/dL}$ [11, 15]

(2) An adrenal venous cortisol concentration after ACTH stimulation ≥ 5 times the cortisol concentration in blood from the inferior vena cava

2) Evaluation criteria for aldosterone hypersecretion and difference between sides

(1) If the adrenal vein plasma aldosterone concentration after ACTH stimulation (measured with the SPAC-S Aldosterone Kit) is $\geq 14,000$ pg/mL (1,400

Fig. 3 Adrenal venography

ng/dL), the adrenal gland on this side is judged to be hypersecreting aldosterone [11, 15]. If the adrenal vein plasma aldosterone concentration is bilaterally $\geq 14,000$ pg/mL, idiopathic hyperaldosteronism is most likely, but there is the possibility of bilateral adenoma or glucocorticoid-remediable aldosteronism, although they are rare [11, 15]. Caution is needed, because criteria of absolute values differ among the assay methods used at various facilities. (2) The adrenal venous blood aldosterone/cortisol (A/C) ratio after ACTH stimulation is calculated bilaterally, and if the lateralized ratio = (adrenal vein A/C ratio on the high-value side) $\div$ (adrenal vein A/C ratio on the low-value side) is ≥ 2.6 , a unilateral lesion is considered to be present on the high-value side [14]. Also, as aldosterone production in the contralateral normal adrenal gland is suppressed in typical unilateral disease, the contralateral ratio = (adrenal vein A/C ratio on the low-value side) $\div$ (adrenal vein A/C ratio on the high-value side) is < 1 . Since the bilateral adrenal venous blood is diluted to different degrees depending on the position of the catheter tip, this method estimates the aldosterone concentration before dilution by assuming that the bilateral adrenal venous cortisol concentrations are equal and correcting the aldosterone concentration for the cortisol concentration.

Caution:

If the results of evaluations (1) and (2) disagree in the same patient, the site of the lesion may also be decided by considering the results of imaging studies.

Notes:

- (1) Glucocorticoid-remediable aldosteronism (GRA) is a very rare disease. GRA should be considered in patients with PA due to autosomal dominant inheritance, those with a childhood onset, those who resist both surgical and medical treatment, etc.
- (2) If the results of the dexamethasone-suppression test suggest autonomous cortisol secretion, adrenal vein catheterization is not evaluated based on the cortisol concentration, and evaluation criteria based on the A/C ratio are not used.

VI. Treatment

Since treatment for PA differs among disease types, disease typing is important.

- 1) If aldosterone hypersecretion from one adrenal has been identified as the cause of PA by AVS, the condition is an indication for laparoscopic adrenalectomy. This surgery can be performed by: (1) a transperitoneal approach (transperitoneal anterior or lateral approach), or (2) retroperitoneal approach (retroperitoneal lateral or posterior approach) [18, 19]. Patients are recommended to undergo laparoscopic surgery by an appointed specialist at an experienced facility. The Japanese Urological Association and Japanese Society of Endourology and ESWL have a system for the certification of urological laparoscopic skills and provide a list of authorized physicians on their home page (<http://square.umin.ac.jp/jsee/>). After adrena-

lectomy, the final diagnosis is made pathologically. Since both APA and IHA exhibit hyperplasia of the zona glomerulosa of the adrenal cortex on H-E staining, immunohistochemical staining of steroid synthetases is important for the differential diagnosis of APA, particularly to distinguish small APA and IHA. Frozen sections are necessary for the staining of aldosterone synthetase, but a diagnosis is also possible from 3β -hydroxysteroid dehydrogenase (3β -HSD) staining of formalin-fixed specimens [20]. In IHA, aldosterone synthetase (P450_{aldo}, CYP11B2) and 3β -HSD are positive in the hyperplastic zona glomerulosa, but the expression of CYP11B2 and 3β -HSD is attenuated in hyperplasia of the zona glomerulosa of the normal tissue, associated with APA.

- 2) If bilateral aldosterone hypersecretion is the cause of PA, or if the disease has been diagnosed as unilateral, but surgery is impossible or is not desired by the patient, medical treatment using MR antagonists is recommended.

***Supplementary comments for Fig.2-2 (*22-25)
(for specialist medical facilities)***

*22: If aldosterone hypersecretion from the unilateral adrenal gland has been established, surgery is indicated.

*23: If a lesion in the contralateral adrenal gland has been excluded, the basic approach is total adrenalectomy of the affected side. Even if there is a tumor in the affected adrenal gland, it may not be an aldosterone-producing adenoma, and there is the possibility of the presence of small aldosterone-producing adenomas not detected by imaging techniques at sites other than the tumor. Therefore, total adrenalectomy instead of enucleation of the tumor should be selected, in principle.

*24: If aldosterone hypersecretion from both adrenal glands has been established, drug therapy is the basic treatment.

However, if on imaging a tumor is noted in one adrenal gland, and the possibility of a cortisol-producing or malignant tumor cannot be excluded, unilateral adrenalectomy should also be considered. Also, patients in whom no tumor is noted at diagnosis should be followed up against the future appearance of an adrenal tumor.

*25: There is no drug therapy that has been confirmed to improve the long-term prognosis, but MR antagonists such as spironolactone and eplerenone should be

primarily used, and antihypertensive drugs such as Ca channel blockers should be added, if necessary (There are reports on the suppressions of aldosterone secretion by Ca antagonists).

VII. Summary

It has been found that the incidence of PA is higher than has been previously considered, and that about 10% of hypertensive patients have this condition [5-10]. These guidelines are based on presently available and reliable data, in the hope that they will help physicians diagnose the disease and investigate treatment to mitigate its effects. There are a number of reports from overseas, some of which are not cited in the guidelines, and a review article on this disease [21] is recommended to improve understanding of it.

VIII. Acknowledgements

This work was partly supported by the Grant for Research on Intractable Diseases provided from the Japanese Ministry of Health, Labour and Welfare, and proceeded by Dr. Jun Saito, Yokohama Rosai Hospital as a medical writer. We thank Dr. John W. Funder (Prince Henry's Institute of Medical Research, Victoria, Australia) for critically reading and for providing valuable suggestions.

IX. Disclaimer

Guidelines are developed to be of assistance to endocrinologists by providing guidance and recommendations for particular areas of practice. The Guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The Guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The Guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of healthcare providers and each patient's individual circumstances.

The Japan Endocrine Society makes no warranty, express or implied, regarding the Guidelines and specifically excludes any warranties of merchantability and fitness for a particular use or purpose. The Society shall not be liable for direct, indirect, special, incidental, or consequential damages related to the use of the information contained herein.

References

1. Takeda R, Matsubara T, Miyamori I, Hatakeyama H, Morise T (1995) Vascular complications in patients with aldosterone producing adenoma in Japan: Comparative study with essential hypertension. *J Endocrinol Invest* 18: 370-373.
2. Nishimura M, Uzu T, Fujii T, Kuroda S, Nakamura S, Inenaga T, Kimura G (1999) Cardiovascular complications in patients with primary aldosteronism. *Am J Kidney Dis* 33: 261-266.
3. Tanabe A, Naruse M, Naruse K, Hase M, Yoshimoto T, Tanaka M, Seki T, Demura R, Demura H (1997) Left ventricular hypertrophy is more prominent in patients with primary aldosteronism than inpatients with other types of secondary hypertension. *Hypertens Res* 20: 85-90.
4. Sherwin RP and Conn JW (1964) Present status of pathology of adrenal gland in hypertension. *Am J Surg* 107: 136-143.
5. Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, Young WF Jr, Montori VM (2008) Case detection, diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 93: 3266-3281.
6. Nishikawa T and Omura M (2000) Clinical characteristics of primary aldosteronism: its prevalence and comparative studies on various causes of primary aldosteronism in Yokohama Rosai Hospital. *Biomed Pharmacother* 54: S83-85.
7. Omura M, Saito J, Yamaguchi K, Kakuta Y, Nishikawa T (2004) Prospective study on the prevalence of secondary hypertension among hypertensive patients visiting a general outpatient clinic in Japan. *Hypertens Res* 27: 193-202.
8. Naruse M, Tanaka T, Otani S, Ogawa J, Tanabe M, Ishizuka N (2009) PHAS-J Study Group--A study on the frequency of PHAS in hypertensive patients in Japan using the network of the National Hospital Organization (NHO). *Nippon Naibunpi Gakkai Zasshi* 85: 246S. (In Japanese)
9. Komiya I, Yamada T, Takasu N, Asawa T, Akamine H, Yagi N, Nagasawa Y, Ohtsuka H, Miyahara Y, Sakai H, Sato A, Aizawa T (1997) An abnormal sodium metabolism in Japanese patients with essential hypertension, judged by serum sodium distribution, renal function and renin-aldosterone system. *J Hypertens* 15: 65-72.
10. Committee for the Preparation of Guidelines for the Treatment of Hypertension, Japanese Society of Hypertension. *Guidelines for the Treatment of Hypertension 2009*. Life Science Publishing, Tokyo, 2009. (In Japanese)
11. Omura M, Sasano H, Saito J, Yamaguchi K, Kakuta Y, Nishikawa T (2006) Clinical Characteristics of aldosterone-producing microadenoma, macroadenoma, and idiopathic hyperaldosteronism in 93 patients with primary aldosteronism. *Hypertens Res* 29: 883-889.
12. Hiramatsu K, Yamada T, Yukimura Y, Komiya I, Ichikawa K, Ishihara M, Nagata H, Izumiyama T (1981) A screening test to identify aldosterone-producing adenoma by measuring plasma renin activity: results in hypertensive patients. *Arch Intern Med* 141: 1589-1593.
13. Tanabe A, Naruse M, Takagi S, Tsuchiya K, Imaki T, Takano K (2003) Variability in the renin/aldosterone profile under random and standardized sampling conditions in primary aldosteronism. *J Clin Endocrinol Metab* 88: 2489-2494.
14. Satoh F, Abe T, Tanemoto M, Nakamura M, Abe M, Urano A, Morimoto R, Sato A, Takase K, Ishidoya S, Arai Y, Suzuki T, Sasano H, Ishibashi T, Ito S (2007) Localization of aldosterone-producing adrenocortical adenomas: Significance of adrenal venous sampling. *Hypertens Res* 30: 1083-1095.
15. Omura M, Sasano H, Fujiwara T, Yamaguchi K, Nishikawa T (2002) Unique cases of unilateral hyperaldosteronism due to multiple adrenocortical micronodules, which can only be detected by selected adrenal venous sampling. *Metabolism* 51: 350-355.
16. Nomura K, Kusakabe K, Maki M, Ito Y, Aiba M, Demura H (1990) Iodomethylnorcholesterol uptake in an aldosteronoma shown by dexamethasone-suppression scintigraphy: relationship to adenoma size and functional activity. *J Clin Endocrinol Metab* 71: 825-830.
17. Nawata A, Takayanagi R, Miura K, Nakagawa H (1999) National Epidemiological Survey of Adrenal Hormone Production Abnormalities in the 1998 Research Reports by the Investigation and Research Group on "Adrenal Hormone Production Abnormalities" as a disease specified by the Ministry of Health, Labour and Welfare. 11-55. (In Japanese)
18. Ishidoya S, Ito A, Sakai K, Satoh M, Chiba Y, Sato F, Arai Y (2005) Laparoscopic partial versus total adrenalectomy for aldosterone-producing adenoma. *J Urol* 174: 40-43.
19. Tanaka M, Okegawa T, Sakai H, Tamaru S, Yoshida M, Imai T (2008) Guidelines for Laparoscopic Adrenalectomy for Adrenal Tumors. *Jpn J Endourol ESWL* 21: 3-14. (In Japanese)
20. Sasano H (1994) Localization of steroidogenic enzymes in adrenal cortex and its disorders. *Endocr J* 41: 471-482.
21. Nishikawa T, Saito J and Omura M (2007) Review Article-Prevalence of primary aldosteronism: Should we screen for primary aldosteronism before treating hypertensive patients with medication? *Endocr J* 54: 487-495.