Roles of Clinical Criteria, Computed Tomography Scan, and Adrenal Vein Sampling in Differential Diagnosis of Primary Aldosteronism Subtypes

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Context: In patients with primary aldosteronism (PA), it is fundamental to distinguish between subtypes that benefit from different therapies. Computed tomography (CT) scans lack sensitivity and specificity and must be followed by adrenal venous sampling (AVS). Because AVS is not widely available, a list of clinical criteria that indicate the presence of an aldosterone-producing adenoma (APA) has been suggested.

Objective and Design: The objective of the study was to test the sensitivity and specificity of the last generation CT scans, test prospectively the usefulness of clinical criteria in the diagnosis of APA, and develop a flow chart to be used when AVS is not easily available.

Setting: Hypertensive patients referred to our hypertension unit were included in our study.

Patients: Seventy-one patients with confirmed PA participated in our study.

Intervention: All patients had a CT scan and underwent AVS.

Main Outcome Measure: Final diagnosis of APA was the main measure.

Results: A total of 44 and 56% of patients were diagnosed as having an APA and a bilateral adrenal hyperplasia (BAH), respectively. Twenty percent of patients with PA displayed hypokalemia. CT scans displayed a sensitivity of 0.87 and a specificity of 0.71. The posture test displayed a lower sensitivity and specificity (0.64 and 0.70, respectively). The distribution grades of hypertension were not significantly different between APA and BAH. Biochemical criteria of high probability of APA displayed a sensitivity of 0.32 and a specificity of 0.95.

Conclusions: This study underlines the central role of AVS in the subtype diagnosis of PA. The use of the clinical criteria to distinguish between APA and BAH did not display a satisfactory diagnostic power. (J Clin Endocrinol Metab 93: 1366–1371, 2008)

Primary aldosteronism (PA) is the most frequent form of secondary hypertension, accounting for up to 5–10% of all hypertensive patients (1). The rate of diagnosis of PA has dramatically increased after the widespread use of the plasma aldosterone (PAC) to plasma renin activity (PRA) ratio as a screening test (2). The diagnosis of PA should not be missed because it has been recently demonstrated that patients with PA exhibit a higher rate of cardiovascular complications, target organ damage, and metabolic syndrome, compared with matched essential hypertensives (3–5). A positive PAC to PRA ratio should always

Abbreviations: A/C, Aldosterone to cortisol ratio; APA, aldosterone-producing adenoma; ARR, aldosterone to PRA ratio; AVS, adrenal venous sampling; BAH, bilateral adrenal hyperplasia; CT, computed tomography; MR, mineralocorticoid receptor; PA, primary aldosteronism; PAC, plasma aldosterone; PRA, plasma renin activity.
be followed by a suppression test to confirm the diagnosis definitively (1). After confirming the diagnosis of PA, it is fundamental to distinguish between subtypes that benefit from surgery and subtypes that should be treated with mineralocorticoid receptor (MR) antagonists (1). In fact, hypertensive individuals with aldosterone-producing adenomas (APA) can be cured or can at least experience significant amelioration of the disease by unilateral adrenalectomy (1, 2, 6), whereas patients with bilateral adrenal hyperplasia (BAH) benefit from targeted pharmacotherapy with MR antagonists (1, 7). Rarer forms of PA are primary adrenal hyperplasia or unilateral hyperplasia that physiologically and biochemically mimic APA and benefit from surgery (8), glucocorticoid-remediable aldosteronism that is a familial form with an autosomal dominant inheritance pattern, which benefits from medical therapy with glucocorticoids (9, 10) and aldosterone-producing adrenal carcinoma. A computed tomography (CT) scan is considered the preferred imaging technique, but because it lacks sensitivity and specificity (11, 12), it must be followed by adrenal venous sampling (AVS), which defines the patients that should undergo unilateral adrenalectomy (1). In fact, CT scanning may miss small adenomas (less than 10 mm) and may identify a nonsecreting nodule in a patient with BAH as an APA. Because AVS is dependent on the radiologist’s experience and is not widely available, some authors have suggested a list of clinical criteria that indicate a high probability of a patient being affected by an APA (13) [in particular, the presence of grade 3 or resistant hypertension, profound hypokalemia (<3.0 mEq/liter), high plasma (>25 ng/dl), and urinary (>30 µg per 24 h) levels of aldosterone and age younger than 50 yr] were all factors considered to be compatible with a high probability of having an APA.

The aims of the present study were: 1) to test the sensitivity and specificity of the latest generation CT scans performed and read by the same expert radiologist; 2) to test prospectively the usefulness of the clinical criteria of high probability in the diagnosis of APA; and 3) to develop a flow chart to be used after the CT scan in patients with confirmed PA, to reduce the number of patients to be referred to other centers for AVS if this technique is not easily available for all patients.

Patients and Methods

In the period January 2004 to January 2007, 71 patients with confirmed PA underwent both CT scan of the adrenal glands and AVS. In 12 patients it was necessary to repeat the AVS for unsuccessful cannulation of the right adrenal vein. In one patient the second AVS was also unsuccessful; improvement was defined as achievement of normal blood pressure with a suppression test to confirm the diagnosis definitively (1). After confirming the diagnosis of PA, it is fundamental to distinguish between subtypes that benefit from surgery and subtypes that should be treated with mineralocorticoid receptor (MR) antagonists (1). In fact, hypertensive individuals with aldosterone-producing adenomas (APA) can be cured or can at least experience significant amelioration of the disease by unilateral adrenalectomy (1, 2, 6), whereas patients with bilateral adrenal hyperplasia (BAH) benefit from targeted pharmacotherapy with MR antagonists (1, 7). Rarer forms of PA are primary adrenal hyperplasia or unilateral hyperplasia that physiologically and biochemically mimic APA and benefit from surgery (8), glucocorticoid-remediable aldosteronism that is a familial form with an autosomal dominant inheritance pattern, which benefits from medical therapy with glucocorticoids (9, 10) and aldosterone-producing adrenal carcinoma. A computed tomography (CT) scan is considered the preferred imaging technique, but because it lacks sensitivity and specificity (11, 12), it must be followed by adrenal venous sampling (AVS), which defines the patients that should undergo unilateral adrenalectomy (1). In fact, CT scanning may miss small adenomas (less than 10 mm) and may identify a nonsecreting nodule in a patient with BAH as an APA. Because AVS is dependent on the radiologist’s experience and is not widely available, some authors have suggested a list of clinical criteria that indicate a high probability of a patient being affected by an APA (13) [in particular, the presence of grade 3 or resistant hypertension, profound hypokalemia (<3.0 mEq/liter), high plasma (>25 ng/dl), and urinary (>30 µg per 24 h) levels of aldosterone and age younger than 50 yr] were all factors considered to be compatible with a high probability of having an APA.

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Results

Thirty-one patients (44%) were diagnosed as having an APA and 39 (56%) as having BAH. Clinical characteristics of patients with APA and BAH are described in Table 1. Patients with APA were slightly younger, with lower potassium levels and higher PAC, ARR, and urinary aldosterone levels, compared with patients with BAH. Urinary sodium excretion was similar between the two groups.

Fifty percent of patients with PA (35 of 70) displayed potassium levels of 3.6 mEq/liter or less and 20% (14 of 70) less than 3.0 mEq/liter at the diagnosis. Interestingly, in some cases the examination of the previous medical records of the patients demonstrated a finding of hypokalemia in patients that were normokalemic at the diagnosis. Overall, the number of patients who showed a previous finding of potassium levels of 3.6 or less was 65.7% (46 of 70). However, 25.8% of patients with APA (eight of 31) and 69.2% of patients with BAH (27 of 39) displayed potassium levels greater than 3.6 mEq/liter at the diagnosis.

Two-hundred and seventy patients with evidence of an APA on CT scan had the diagnosis confirmed after AVS, and similarly 28 with BAH had a concordant diagnosis between CT scan and AVS. By considering together, the CT scan and the posture test displayed a sensitivity of 0.48, a specificity of 0.93, and positive and negative predictive values of 0.82 and 0.72, respectively.

The distribution of grade 1, 2, and 3 and resistant hypertension (17) was not significantly different between the two subtypes of PA (Fig.1). In particular, 48% of patients with APA and 51% with BAH displayed hypertension grade of 3 or higher.

Hypokalemia (<3.6 mEq/liter) was present in 74.2% of patients with APA (23 of 31) and 30.8% of patients with BAH (12 of 39), whereas marked hypokalemia (<3 mEq/liter) was present in 38.7% of patients with APA (12 of 31) and 5.1% of patients with BAH (2 of 39).

Twenty-nine of 31 patients with a final diagnosis of APA (93%) and 23 of 39 with BAH (59%) displayed a PAC greater than 25 ng/dl and/or a urinary aldosterone greater than 30 μg per 24 h.

Eighteen of 31 patients with APA (58%) displayed a unilateral nodule of 10 mm or greater on CT scan with a normal adrenal in the contralateral side, but six of 39 patients with BAH (16%) displayed similar CT findings and therefore might have been inappropriately adrenalectomized if the decision had been based entirely on the data of the CT scan. After surgery 21 of 31 adrenals (68%) displayed dimension of 10 mm or greater, whereas the remaining 10 (32%) were microadenomas.

Considering together two or more of the criteria of high probability of APA, we observed that 10 of 31 patients with APA (32%) and two of 39 of patients with BAH (5%) had both hypokalemia (<3 mEq/liter) and high aldosterone levels (PAC > 25 ng/dl and/or a urinary aldosterone greater than 30 μg per 24 h).

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<th>TABLE 1. Biochemical and hormonal parameters of the patients with PA</th>
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<td>Age (yr)</td>
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<td>Dimension of APA (mm)</td>
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<td>sK⁺ at diagnosis (mEq/liter)</td>
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<td>sK⁺ minimum recorded (mEq/liter)</td>
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<td>Upright PAC (ng/dl)</td>
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<td>Upright ARR (ng/ml⁻¹×ng ml⁻¹×h⁻¹)</td>
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<td>Recumbent ARR (ng/ml⁻¹×ng ml⁻¹×h⁻¹)</td>
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<td>Urinary aldosterone (μg/d)</td>
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<td>Urinary Na⁺ (mEq/d)</td>
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Parameters are shown as mean ± SD (when normally distributed) or as median (25th to 75th percentile). sK⁺, Serum potassium; Na⁺, sodium; SLT, saline load test.
The relatively high prevalence of PA and the high rate of cardiovascular complications make it important for the clinician not to miss the diagnosis of PA. One of the most challenging aspects is the differentiation between the two major subtypes of PA: this is of particular importance because optimal treatment for patients with APA is unilateral adrenalectomy, whereas patients with BAH are best treated with specific medical therapy with MR antagonists. AVS is considered the gold standard for the determination of the patients with surgically treatable forms of PA; however, this technique requires experienced radiologists and is available in only a few centers. Furthermore, it is a highly costly and invasive technique. For this reason some authors developed flow charts aimed at reducing the numbers of AVS in patients with PA. In this study we reevaluated the diagnostic performance of the CT scan when performed by the same highly motivated radiologist using the latest generation apparatus and of the posture test; furthermore, we prospectively investigated the potential role of different clinical and biochemical criteria in the differential diagnosis between APA and BAH.

We demonstrated that under our conditions, CT scan provided useful information and was concordant with AVS in a much higher proportion (77%) than previously described (9). Interestingly, all patients with a unilateral macronodule (<1 cm) and young age (<40 yr) were found to have APA. This is in agreement with the low prevalence of nonsecreting adrenal tumours (incidentaloma) in young subjects (18) and in agreement with the recommendation of some authors that adrenalectomy be undertaken without the need to perform AVS in these patients (19) (Fig. 3). However, the current study should not be regarded as confirmatory for such a recommendation because only five patients displayed these characteristics, and therefore, a prospective study in a wider population of PA should be performed before considering this indication as definitive. In fact, because our population includes selected patients, it is conceivable that less florid forms of PA, including normokalemic patients, may
It is nevertheless the best currently available way to guide therapy for a patient with PA. In fact, a small proportion of patients with unilateral secretion may be affected by a unilateral hyperplasia (primary adrenal hyperplasia) and not by an APA, but this would not change the indication to adrenalectomy. In the rare case of bilateral APA, which is hard to distinguish from BAH with bilateral macronodules, the AVS would result in a bilateral form of PA, indicating medical therapy.

In conclusion, our data confirm that definitive differentiation of subtypes in patients with PA is most reliably achieved with AVS. However, when CT scanning is performed by a highly motivated radiologist using a fine cut of the adrenal glands, AVS, if not easily available, can be avoided in some selected cases. This may be the case for very young patients with a macronodule on the CT scan and a normal appearance of the contralateral gland, in which adrenalectomy can be considered, and for patients with bilaterally normal appearance of the adrenal glands in which a medical treatment with spironolactone can be considered without performing AVS. It should be emphasized that these suggestions should be applied only to those units in which AVS cannot be performed routinely. Furthermore, in the case of bilaterally normal adrenal glands, the presence of criteria of high probability of APA (high aldosterone + low potassium + hypertension ≥ grade 3) or the wish of the patient to have the possibility of a surgical cure definitively confirmed or excluded should nonetheless prompt performance of AVS.

Acknowledgments

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References


comprise patients of younger than 40 yr of age with a unilateral macronodule on CT and affected by BAH.

We also observed that only in one of 22 patients with a bilaterally normal appearance of the adrenal glands subsequently were found to have APA after AVS. When AVS is not easily available and/or there is the necessity of reduction of costs, treatment with MR antagonists in these patients is a reasonable option (Fig. 3). In all other patients with PA, AVS is indispensable for the differentiation between surgically treatable forms of PA and forms that should be treated with MR antagonists.

It is noticeable that in all patients with an APA except one, it was possible to demonstrate an alteration of the adrenal morphology on CT, suggesting that the sensitivity of this technique is improved when used by an expert and motivated radiologist; by contrast, the specificity of the CT scan remains low because the morphological description cannot help in determining the secretory function of the observed lesion.

We also showed that the posture test is not useful in differentiating APA from BAH because 33% of patients were not correctly classified with this test, in accordance with previous findings (2). In fact, it has been demonstrated, that 30–50% of APA respond to angiotensin II stimulation, and similarly 30% of patients with BAH do not display a significant increase in aldosterone levels after angiotensin II stimulation (20).

Unfortunately, none of the criteria of high probability for APA allows the avoidance of AVS and successfully distinguishes APA from BAH. However, patients who simultaneously display high aldosterone levels together with severe hypertension and severe hypokalemia are more often affected by APA.

Interestingly, 38% of patients with APA did not display, at the moment of the diagnosis, either hypokalemia or severe or resistant hypertension and therefore would have been missed if only these conditions were considered as prerequisite to screen the patient for PA; this is in agreement with the findings of other authors (20) and indicates that a wider application of the ARR to hypertensive patients is needed to provide the opportunity of detection and surgical cure to all patients with APA.

A limitation of the present study is that, despite the fact that it has been performed prospectively, it suffers from potential selection bias, in that many patients included in the study were referred to our centers for very high ARR and/or hypokalemia. This could explain the higher proportion of APA and hypokalemia, compared with patients uniquely screened in a single center (20). It should also be noted that whereas AVS is not perfect, it is nevertheless the best currently available way to guide therapy...