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RESEARCH LETTER

Evolution of computed tomography-detectable adrenal nodules in patients with bilateral primary aldosteronism

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Introduction

Computed tomography (CT) appearance of adrenals in primary aldosteronism (PA) ranges from normal to bilateral diffuse enlargement or nodular glands. Idiopathic hyperaldosteronism (IHA) due to bilateral autonomous production of aldosterone (bilateral PA) is the most common subtype of PA, accounting for 50–70 % of PA patients [1, 2]. Regardless of adrenal image findings, IHA is diagnosed by adrenal venous sampling (AVS) in PA patients who do not show lateralization of aldosterone secretion [3], and is treated by long-term medical therapy using mineralocorticoid receptor antagonists. The other common PA subtypes, aldosterone-producing adenoma (APA) and unilateral adrenal hyperplasia, display lateralization of aldosterone secretion at AVS and are treated by unilateral adrenalectomy. Natural course of adrenal mass lesions in IHA patients has not yet been fully clarified. The aim of our study was to assess the over time evolution of CT-detectable adrenal nodule(s) in bilateral PA.

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Materials and methods

Thirty-two patients (23 males and 9 females; age 50 ± 9 years, as mean ± SD) diagnosed as IHA in our institutions during the last 6 years and regularly seen in our outpatient clinics at follow-up after diagnosis were recruited on the basis of their medical records, indicating the presence of nodular adrenal lesions. Each subject provided informed consent for the study, which was approved by local Ethics Committees. Clinical and biochemical characteristics of patients at diagnosis and follow-up are summarized in Table 1. Screening and confirmation of PA were performed in agreement with the Endocrine Society guidelines [2], as described previously [4]. Briefly, for the diagnosis of PA, all patients with an upright plasma aldosterone to PRA ratio (ARR) >40 (aldosterone in ng/dL and PRA in ng/mL/h), in the presence of aldosterone >15 ng/dL and suppressed PRA, underwent saline infusion (0.9 % NaCl 500 mL/h for 4 h) as a confirmatory test. Patients with plasma aldosterone levels that did not fall below 5 ng/dL after the saline infusion were diagnosed as having PA. In all patients, an adrenal CT scan with contrast and fine cuts (2.5–3 mm) was performed using standardized criteria, commonly used for adrenal gland investigations [5]. Adrenal was described as nodular when unilateral or bilateral nodule(s) of at least 8 mm in diameter, measuring the thickness of the body of the gland and of each limb, were detected. The diagnosis of a benign adrenal nodule rested on the following CT criteria: size <4 cm, regular shape with well-defined margins, homogeneous and hypodense content. All CT scans at diagnosis and at follow-up were blinded and independently reviewed by three experienced radiologists. If discordant opinions were recorded, final evaluation was resolved by consensus. Regardless of CT

Table 1 Clinical and biochemical characteristics of patients at diagnosis and follow-up

No.	At diagnosis					Duration of follow-up, months	At follow-up		
	Age (years)/sex	SBP/DBP, mmHg	Ser. K, mmol/L	ARR	CT adrenal mass size (mm)/side		SBP/DBP, mmHg	Ser. K mmol/L	% CT variation of adrenal mass
1	41/M	160/105	3.9	160	15/L	42	120/85	4.6	−17
2	61/M	170/120	3.4	93	15/L	40	140/85	4.1	+33
3	67/M	160/100	3.2	623	10/L, 20/R	39	140/80	4.0	0/L, 0/R
4	64/M	190/110	3.3	101	15/R	71	120/90	4.5	+35
5	54/M	170/110	3.3	81	15/R	72	130/80	3.7	0
6	32/F	160/100	4.0	133	12/L	36	155/85	4.1	0
7	53/M	180/100	3.8	137	10/R	38	170/100	3.8	0
8	52/M	155/95	3.0	76	28/L	40	140/85	3.8	0
9	53/M	150/90	3.5	63	10/L, 8/R	40	130/80	4.5	+10/L, 0/R
10	57/M	175/120	3.5	114	20/L	40	180/100	4.5	+5
11	57/M	185/95	3.5	156	10/L	42	130/80	4.3	0
12	43/M	165/105	3.0	80	13/L	46	130/80	3.9	0
13	46/M	190/110	3.4	52	10/L	63	150/90	4.5	0
14	47/F	165/105	3.0	264	17/R	76	130/90	4.0	0
15	43/F	160/95	3.3	64	8/L, 9/R	69	160/90	4.3	0/L, 0/R
16	55/M	180/100	4.0	131	23/R	67	150/90	4.7	+13
17	41/M	170/100	3.2	53	13/R	70	140/80	3.9	0
18	50/M	145/100	3.9	420	12/L	40	125/75	4.7	0
19	50/M	180/115	4.2	52	27/R	48	130/90	4.2	0
20	40/F	140/80	1.9	634	12/R	39	130/85	4.1	0
21	38/M	160/100	3.4	131	10/L	59	140/90	4.2	+20
22	57/M	145/100	4.0	188	15/L	51	135/85	4.6	0
23	33/F	160/105	3.0	137	10/R	44	120/80	4.0	+10
24	48/F	180/110	4.3	50	20/R	36	110/70	4.5	−5
25	51/M	140/95	4.2	124	8/R	38	110/80	4.2	+14
26	64/F	180/100	4.2	154	25/R	62	150/90	4.6	0
27	57/M	130/95	3.3	142	10/L	60	125/85	4.3	0
28	58/F	150/95	3.8	101	16/L	44	130/70	4.1	0
29	59/M	150/90	2.9	270	12/L	44	100/70	4.4	0
30	41/M	180/100	3.4	450	11/R	46	135/85	4.2	+9
31	66/M	230/110	2.8	138	12/L	65	180/105	4.0	0
32	46/F	190/105	3.5	317	10/L, 8/R	60	130/90	4.2	0/L, 0/R

M male, *F* female, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *ARR* aldosterone to renin ratio, *CT* computed tomography, *L* left, *R* right

findings, an AVS was performed to differentiate between APA and IHA. Sampling was considered successful if the adrenal vein/inferior vena cava cortisol gradient was at least 3; lateralization was considered when the aldosterone to cortisol ratio from one adrenal was at least four times the ratio from the contralateral gland. Hormonal assays were performed as previously described [4]. The presence of the syndrome of glucocorticoid-remediable aldosteronism was excluded by the long polymerase chain reaction test [4].

Results and discussion

All patients with adrenal nodules at diagnosis (median diameter 12 mm, range 8–28 mm; 28 unilateral and 4 bilateral) had CT imaging re-evaluated 3–6 years (median 45 months) after diagnosis. A unilateral nodular lesion enlargement ≥25 % was detected only in two cases (no. 2 and 4), both showing blood pressure normalized by medical treatment. No increase or a change in dosage of antihypertensive drugs previously to adrenal CT control was

observed in these patients. A slight increase, i.e., <25 %, or no variations or a decrease of nodule size occurred in the remaining 30 cases. No patients showed appearance of radiological picture of malignancy or new masses in the ipsilateral/contralateral glands. At follow-up with 6–12 months outpatient visits all patients showed reported compliance to medications, and 29/32 patients had a persistent clinical/biochemical control of the disease. This was defined as the sustained reduction of blood pressure to ≤150/90 mmHg using mineralocorticoid receptor antagonist alone ($n = 8$) or in addition to other antihypertensive agents ($n = 24$), and a stable serum potassium level. Three patients (no. 7, 10, 31) presenting hypertension resistant to a combination of four different antihypertensive drugs, refused to repeat AVS for diagnostic re-assessment. Renal function was normal at initial evaluation, and did not change at follow-up.

While several concordant diagnostic and therapeutic algorithms have been proposed for the management of patients with APA, follow-up studies for patients with bilateral PA are mainly limited to evaluation of cardiocerebrovascular and renal outcome during medical therapy [6, 7]. Few studies reporting over time adrenal morphological and/or functional evolution in patients with this disease are available, and those found in the literature are not univocal, probably on account of different durations of observation, number of patients studied and methodological approaches adopted. Sukor et al. [8], using CT performed serially during a 12–144 months follow-up in 51 patient with PA who underwent unilateral adrenalectomy, did not retrospectively reveal any morphological change in the remaining adrenal gland. Fischer et al. [9] in a retrospective study from German Conn's Registry data showed remission of autonomous aldosterone secretion in 2 out 37 patients treated with mineralocorticoid antagonists at 13 and 11 years follow-up after diagnosis of bilateral aldosteronism, but at initial evaluation both patients did not have adrenal nodules at CT and did not undergo AVS. Lucatello et al. [10] reported retrospective adrenal imaging in 13 out of 34 patients with confirmed bilateral PA at AVS and an adrenal mass at diagnosis, not revealing any significant change in morphology at follow-up. However, no precise radiological definition of adrenal nodule was given and morphological follow-up was less or equal to 1 year in all patients. Furthermore, re-evaluation of aldosterone hypersecretion after withdraw of medical treatment was not performed in combination with morphological follow-up, but at 3-year follow-up.

The major finding of our study concerns the morphological evolution of the adrenal lesions over time. Malignant transformation has been reported in incidentally found non-functioning adrenal adenomas [11], and several mitogenic factors are known to control adrenal growth and aldosterone secretion in unilateral/bilateral aldosteronism [12]. Our CT data showed that adrenal mass enlargement in no case exceeded 3 cm of diameter or was associated with signs of malignant transformation, suggesting that mass increase was casual and not a marker of malignancy. Moreover, due to the paucity of numbers, we could not identify possible basal predictors of size increase, such as initial mass dimensions or functional status. In the great majority of our cases, there was no evidence of an evolution towards a clear clinical/biochemical worsening of the disease, although the shift to unilateral aldosterone hypersecretion could not be completely excluded in patients with hypertension difficult to control. Furthermore, it was not assessed in our patients a spontaneous resolution of IHA or a difference in the growth of adrenal nodules after discontinuation of antihypertensive drugs, including mineralocorticoid receptor antagonists.

The main limitations of our study were the relatively small population size and length of observation. In spite of using common diagnostic procedures, radiological definitions of adrenal morphology and laboratory method, follow-up was also conducted in multiple clinical institutions.

In conclusion, over time CT variations of adrenal nodules are uncommon and without apparent signs of malignancy in patients with AVS-confirmed bilateral PA. A diagnostic reassessment may be advisable in patients with marked changes in adrenal morphology and/or resistant hypertension. Larger studies are needed to assess the utility of long-term surveillance of nodular adrenal lesions in IHA.

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Compliance with ethical standards

Conflict of Interest None.

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