Evaluation of Hormonal Function in a Series of Incidentally Discovered Adrenal Masses

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The discovery of an asymptomatic adrenal mass (incidentaloma) during the investigation of an unrelated condition is relatively common. In this study, we report the clinical, radiologic, and endocrine evaluation of 38 patients (22 women and 16 men aged 24 to 84 years) with adrenal incidentaloma (size, 1 to 12 cm). The patients underwent basal and dynamic evaluation of the hypothalamic-pituitary-adrenal (HPA) axis, renin-angiotensin-aldosterone system, and adrenomedullary function. Moreover, computed tomograpy (CT) scan and ^{131}I-6β-iodomethyl-19-norcholest-5(10)-en-3β-ol (NP-59) and/or ^{131}I-metaiodobenzylguanidine (MIBG) scintigraphy were performed. The endocrine evaluation indicated two cases of pheochromocytoma and four cases of preclinical Cushing's syndrome, three of which underwent surgery with histologic diagnosis of two adrenocortical adenomas and one carcinoma. Low levels of serum dehydroepiandrosterone sulfate (DHEA-S), associated with a markedly increased 17-hydroxyprogesterone (17-OHP) response to a corticotropin (ACTH) test, were found in patients with incidentaloma. On the basis of endocrine and morphologic data, 13 patients underwent surgical treatment: five adrenocortical adenomas (two functioning), two pheochromocytomas, two ganglioneuromas, one cortisol-secreting adrenal carcinoma, one lymphangiomatous cyst, one myelolipoma, and one hemorrhage were found. Careful diagnostic assessment of incidentally discovered adrenal masses must be performed to exclude the presence of malignant and/or functioning lesions and to verify the possibility that patients with incidentaloma have a genetic or acquired deficit of adrenal steroidogenic activity.

THE DISCOVERY of an incidental adrenal mass (incidentaloma) has been relatively common since the wider application of sensitive noninvasive methods to image the abdomen such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI). For this reason, it has come to represent an emerging clinical and biological problem for which the prevalence is approximately 0.7% in abdominal CT scan series[1,2] and between 1.4% and 8.7%[3,4] in unselected autopsy series.

Incidentalomas of the adrenal gland are usually asymptomatic and often classified as nonfunctioning masses. However, most of these tumors may secrete hormones in insufficient amounts to cause clinically apparent disease. There are recent reports[5-7] of several cases of adrenal incidentaloma with no clinical evidence of Cushing's syndrome, normal basal steroid secretion, but nonsuppressible serum cortisol (C) after dexamethasone (DEX) administration. In these cases, which were regarded as "preclinical Cushing's syndrome," adrenalectomy has restored a normal C suppression to DEX. A few cases of asymptomatic pheochromocytoma[3,8] or asymptomatic aldosteronoma[9] have also been reported. Furthermore, the malignant (either primary or metastatic) nature of the adrenal mass[10-12] cannot always be excluded. Recently, some patients with silent adrenal nodules and a mild form of 21-hydroxylase deficiency have been described,[13-14] suggesting a possible pathogenetic role of steroidogenic deficiency in the development of adrenal masses.

To verify the presence of hormonal hypersecretion and/or a defect of steroidogenic activity in clinically silent adrenal masses, we performed screening tests for excess catecholamine (CA), mineralocorticoid, glucocorticoid, and androgen secretion in a series of 38 patients with adrenal incidentaloma.

SUBJECTS AND METHODS

Since 1990, we have examined 38 consecutive patients (22 women and 16 men aged 24 to 84 years; mean ± SEM 58 ± 2.3; median, 57.5) with an unsuspected adrenal mass discovered by abdominal ultrasonography (22 cases), CT scan (15 cases) and x-ray (one case) during general, urologic, or gastroenterologic evaluations or surgery. None of the patients showed specific signs and/or symptoms of hormone excess. Masses discovered during the staging of a malignant disease were excluded. Table 1 reports patient data.

Radiologic Evaluation

All tumors were evaluated by CT scan with intravenous (IV) contrast medium. Twenty-six patients with a mass greater than 2 cm in diameter underwent a ^{131}I-6β-iodomethyl-19-norcholest-5(10)-en-3β-ol (NP-59) adrenal scan in the basal condition. In four cases, sympathoadrenal imaging was performed with ^{131}I-metaiodobenzylguanidine (MIBG).

Endocrine Evaluation

The subjects were admitted to the clinical center at least 3 days before the study, and were maintained on a constant diet containing 90 mEq sodium and 60 mEq potassium per day. Smoking and the use of alcohol, tea, caffeine-containing foods, and hypotensive drugs were prohibited for 10 days before and throughout the study procedure. Baseline hormone levels were measured at 8:00 AM after an overnight fast, with subjects in the supine position at least 8 hours before the test.

Endocrine function was evaluated by the following: (1) measurement of 24-hour urinary excretion of CA (UCA) and vanillylmandelic acid (VMA); (2) measurement of plasma CA levels (four cases); (3) measurement of 24-hour urinary excretion of free cortisol (UFC); (4) measurement of plasma corticotropin (ACTH) and C levels at 8:00 AM and 11:00 PM; (5) measurement of plasma renin activity (PRA) and

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Submitted May 20, 1996; accepted July 22, 1996.

Supported by grants from the Italian National Research Council (Rome, Italy) "Prevention and Control of Disease Factors, sub-project Stress (no. 95.00879, PF41)", the Italian Ministry of University and Scientific and Technological Research (40% to 60%), and Associazione Ferrarese dell'Ipertensione Arteriosa.

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0026-0495/97/4601-0019$03.00/0

plasma aldosterone (PA) levels in clinostatic and orthostatic posture; (6) measurement of serum dehydroepiandrosterone sulfate (DHEA-S), 17-hydroxyprogesterone (17-OHP), androstenedione (A), testosterone (T), and electrolyte levels; (7) an overnight low-dose DEX suppression test (1 mg orally at 11:00 PM and measurement of serum C levels at 8:00 AM the following morning, 32 cases; patients with nonsuppressible C after the overnight suppression test underwent a high-dose suppression test with DEX 8 mg/d for 2 days); (8) an ovine corticotropin-releasing hormone ([oCRH] Clinalfa, Laufelfingen, Switzerland) test (100 μg IV bolus at 8:00 AM, with measurement of serum C and plasma ACTH levels at −15, 0, 15, 30, 45, 60, 90, and 120 minutes, 27 cases); and (9) an ACTH (synthetic ACTH, Synacthen; Laboratories CIBA-GEIGY, Huningue, France) test (250 μg IV bolus at 8:00 AM, with measurement of serum C, 17-OHP, and DHEA-S levels at −15, 0, 15, 30, 45, 60, 90, and 120 minutes, 30 cases). The ACTH test was performed in the early follicular phase in premenopausal women.

Blood pressure (BP) was monitored in all patients for 24 hours by an automated noninvasive instrument (Spacelabs 90207; Kontron Instruments, Milan, Italy).

Hormonal values were determined by radioimmunoassay (RIA) or immunoradiometric assay (IRMA) methods using commercially available kits. Plasma CA, UCA, and VMA levels were measured using high-performance liquid chromatography with electrochemical detection, with materials and instrumentation supplied by Bio-Rad Laboratories (Hercules, CA). Intraassay and interassay coefficients of variation for plasma epinephrine (E) were 4% and 5.3%, respectively, for plasma norepinephrine (NE) 4.1% and 6%, respectively, and for UCA and VMA less than 4% and 12%, respectively. UFC and serum C were determined by RIAs using material supplied by Clinical Assays, a Division of Travenol Laboratories (Cambridge, MA). DHEA-S, 17-OHP, A, T, and PA were determined by RIAs using material supplied by Diagnostic Products (Los Angeles, CA). PRA level was measured by RIA using material supplied by Sclavo (Siena, Italy). Plasma ACTH level was measured by IRMA using material supplied by Nichols Institute (San Juan Capistrano, CA). Intraassay and interassay coefficients of variation for all the methods were less than 5% and 11%, respectively.

The normal ranges for these values in our laboratory are as follows: ACTH, 1.5 to 11.5 pmol/L; C, 0.14 to 0.7 μmol/L; PA, less than 0.41 nmol/L and 0.1 to 0.83 nmol/L in clinostatic and orthostatic posture; PRA, 0.05 to 0.55 ng/L/s and 0.42 to 1.4 ng/L/s in clinostatic and orthostatic posture; A, 1 to 11 nmol/L in males and 0.7 to 8 and 1.2 to 6.3 nmol/L in females in premenopause (pre-MP) and postmenopause (post-MP); DHEA-S, 2.5 to 14 μmol/L for age less than 40 years, 2.5 to 11 μmol/L for 40 to 49 years, and 1.6 to 6.8 μmol/L for more than 50 years in males; DHEA-S, 1.9 to 8.8 and 1.1 to 5.3 μmol/L in females pre- and post-MP; 17-OHP, 1.2 to 7.6 nmol/L in males and 0.9 to 3.6 and 0.3 to 1.8 nmol/L in females in pre- and post-MP; and UFC, less than 373 nmol/d.

Sodium and potassium levels were measured by flame photometry, using lithium as internal standard.

A percent ratio for C less than 50% between levels recorded at 11:00 PM and 8:00 AM was considered a normal diurnal rhythm. The overnight low-dose DEX suppression test was considered normal when morning C levels were less than 0.09 μmol/L.[15] An increase of plasma ACTH and serum C greater than 4.4 pmol/L and 0.2 μmol/L, respectively, was considered a normal response to the oCRH test. Basal serum levels of C, DHEA-S, and 17-OHP and their responses to the ACTH test were compared with those obtained in a group of 25 healthy subjects (controls: 15 females with a mean age of 47 years, pre-MP in early follicular phase, and 10 males with a mean age of 50 years).

Patients who had a mass size greater than 4 cm, CT characteristics suggestive[16] of malignancy (irregular margins, intratumoral necrosis or hemorrhage, calcifications, inhomogeneous enhancement after IV contrast, and evidence of hepatic, nodal, or venous spread), absent uptake to NP-59 scan, enlargement of mass size on follow-up evaluation, and/or hormonal hypersecretion were submitted to surgery.

A 6- to 18-month follow-up study performed in 14 patients with unoperated incidentaloma included CT scan, measurements of UFC, ACTH, C, and DHEA-S levels, and an overnight low-dose DEX suppression test. A basal evaluation of adrenal function was also repeated in all the operated incidentalomas, and a DEX suppression test was performed in adenomas. The ACTH test was repeated only in operated incidentalomas that previously presented an elevated 17-OHP response.

Statistical Analysis

ANOVA was used for comparison of mean hormone levels between the times of assessment. Duncan's multiple-range test was used to determine the location of significant differences in mean values. Time-matched comparisons of C, 17-OHP, and DHEA-S levels between the control group and patients were assessed using a paired Student's t test. Data are reported as the mean ± SEM. P less than .05 was accepted as statistically significant.

RESULTS

Clinical and radiologic characteristics and some endocrine data in the patients with incidental adrenal masses are shown in Table 1. Mass size ranged from 1 to 12 cm (median, 2.55). Incidentalomas were unilateral in 28 cases and bilateral in 10 cases. NP-59 scintigraphy showed unilateral uptake to the side of the adrenal mass in nine cases and bilateral uptake with a prevalence to the side of the mass in nine cases (concordant pattern), bilateral symmetric uptake in four cases (nonlateralizing scan), no uptake to the side of the mass in three cases (discordant pattern), and bilaterally absent uptake in one case. The MIBG scan was negative in three patients (no. 6, 15, and 35) and positive in one (no. 16) with normal UCA and plasma CA levels and histologic diagnosis of ganglioneuroma. Nine patients (23.6%) had mild hypertension with mean values of 158 ± 5.7 and 99 ± 4.3 mm Hg for systolic and diastolic BP, respectively; nine (23.6%) had obesity; two (5.2%) had non–insulin-dependent diabetes mellitus; and 13 (36.8%) had goiter.

UCA and VMA excretion was elevated in one patient (no. 15) with histologic diagnosis of pheochromocytoma. This patient had normal BP with no circadian variability and slightly elevated plasma CA levels (E 0.39 nmol/L and NE 3.43 nmol/L; normal values, E < 0.36 nmol/L and NE 0.5 to 2.65 nmol/L), which increased (peak, 0.5 nmol/L for E and 6.65 nmol/L for NE at 120 minutes) after clonidine administration (300 μg orally), and a negative MIBG scan. In this patient, a normal circadian rhythm for BP and a normal response of plasma CA to clonidine (E 0.1 nmol/L and NE 1.16 nmol/L in the basal condition, and E < 0.054 nmol/L and NE 0.56 nmol/L after clonidine) were observed after surgery. The patient (no. 37) bearing a silent pheochromocytoma was referred to our department in the postsurgery period, after monolateral adrenalectomy for an incidentally discovered mass during a general check-up. This patient had only a mild hypertension, which was unchanged after adrenalectomy.

All patients, except case no. 33 with a low basal level of ACTH and high UFC, showed normal levels of UFC, normal values for serum C, PA, PRA, A, T, and electrolytes, and a normal diurnal rhythm for the C secretory pattern.

Mean plasma ACTH and C responses to oCRH administra-

tion in all patients were not different from those observed in normal subjects, except in three patients (cases no. 29, 32, and 33) in which the peak level of ACTH was lower than expected. Two patients (cases no. 2 and 5) with bilateral nodular hyperplasia showed basal levels of plasma ACTH in the low-normal range with a normal response to the oCRH test (Table 1).

Basal values for DHEA-S in patients with incidentaloma (range, 0.23 to 10.79 μmol/L; mean ± SEM, 1.69 ± 0.36) were significantly lower ($P < .05$) than those observed in the controls (range, 0.49 to 11.50 μmol/L; mean ± SEM, 4.63 ± 1.25). Serum DHEA-S levels did not significantly change after ACTH stimulation in normal subjects or in patients with incidentaloma. Mean basal levels of serum 17-OHP and C in patients with incidentaloma (2.36 ± 0.57 nmol/L and 0.43 ± 0.04 μmol/L, respectively) did not differ from those in the normal subjects (2.63 ± 0.24 nmol/L and 0.46 ± 0.04 μmol/L, respectively). The response of 17-OHP to ACTH (Fig 1) was elevated in 19 of 30 patients, with a mean peak of 16.79 ± 1.62 nmol/L at 60 minutes, significantly ($P < .01$) different from that observed in controls (5.9 ± 0.33 nmol/L).

Patients no. 29, 32, and 38 exibited the biochemical characteristics of preclinical Cushing's syndrome: plasma ACTH levels in the low-normal range, normal levels of serum C and UFC, normal diurnal rhythm of C secretion, nonsuppressible C to DEX (high-dose), and low levels of DHEA-S (Table 1). Moreover, these subjects (Table 1 and Fig 1) showed an exaggerated response of serum C and 17-OHP to the ACTH test (17-OHP at 60 minutes > the level of 15 nmol/L considered normal in the healthy population).[17] They had unilateral uptake

Table 1. Clinical and Radiologic Features and Some Endocrine Data in 38 Patients With Adrenal Incidentaloma

Case No.	Age (yr)	Sex	Side	Size (cm)	CT Density	NP-59 Scan	MIBG Scan	DHEA-S	Dex		ACTH		C After		Histologic Diagnosis
									1 mg	8 mg	Basal	After oCRH	oCRH	ACTH	
1	55	M	Right	4.2	Hypo	H		L	S		N	N	N	N	Adrenal adenoma
2	49	F	Bilat	1.8	Hypo			N	S		L	N	N	N	
3	72	F	Bilat	2.2	Hypo	H		L	S		N	N	N	N	
4	74	M	Right	2.5	Hypo						N				
5	62	F	Bilat	3.0	Hypo	N		L	S		L	N	N	N	
6	33	F	Left	5.0	Hypo	A	Neg	L			N				Lymphangiomatous cyst
7	76	M	Bilat	2.5	Hypo	N		N	S		N	N	N	N	
8	80	F	Right	3.4	Inhom	N		L	S		N	N	N	N	FNA: inconclusive
9	24	M	Right	1.1	Hypo			N	S		N	N	N	N	
10	40	F	Right	1.2	Hypo			N	S		N	N	N	N	
11	70	M	Right	1.5	Hypo			N			N				
12	56	M	Bilat	4.3	Hypo	H		N	S		N	N	N	N	Adrenal adenoma
13	55	F	Bilat	3.6	Hypo	H		L	S		N	N	N	N	
14	62	F	Left	3.0	Hypo	H		L	S		N	N	N	N	
15	50	M	Right	2.1	Inhom	N	Neg	L	S		N				Pheochromocytoma
16	47	M	Right	2.6	Inhom	A	Pos	N	S		N				Ganglioneuroma
17	58	F	Bilat	3.0	Hypo	N		N	S		N	N	N	N	
18	56	F	Left	1.5	Hypo			N			N				
19	47	F	Right	2.5	Hypo	N		L	S		N				
20	58	F	Right	4.5	Hypo	H		N	S		N	N	N	N	Adrenal adenoma
21	38	M	Left	3.5	Inhom	N		L			N	N	N	N	Ganglioneuroma
22	69	M	Bilat	3.8	Hyper	N		N	S		N	N	N	N	FNA: adrenal hyperplasia
23	70	F	Bilat	3.0	Hypo	N		N	S		L	N	N	N	
24	62	M	Left	1.5	Hyper			N	S		N			N	
25	64	M	Bilat	2.0	Hypo			L	S		N	N	N	N	
26	64	M	Left	1.9	Hypo			L	S		N			N	
27	54	F	Left	1.8	Hypo			N	S		N	N	N	N	
28	72	M	Right	4.0	Hypo	N		N	S		N			N	
29	84	F	Left	4.0	Hypo	H		L	NS	NS	L	L	L	H	
30	55	F	Right	2.5	Hyper	N		N	S		N	N	N	N	Hemorrhage
31	66	F	Left	2.5	Hyper	N		L	S		N	N	N	N	
32	37	F	Right	4.5	Hypo	H		L	NS	NS	L	L	L	H	Adrenal adenoma
33	46	F	Left	12	Inhom	A		N	NS	NS	L	L	L	H	Adrenal carcinoma
34	51	M	Right	1.0	Hypo			N	S		N	N	N	N	
35	51	M	Right	8.0	Hypo	A	Neg	L	S		N	N	N	N	Myelolipoma
36	57	F	Left	2.5	Hypo	N		L	S		N	N	N	N	
37	75	F	Left	10	Inhom										Pheochromocytoma
38	66	F	Right	2.5	Hypo	H		L	NS	NS	L	N	N	H	Adrenal adenoma

NOTE. For the NP-59 scan, normal means symmetric bilateral uptake of NP-59 (cases no. 7, 15, 21, and 30) or bilateral uptake with prevalence for the side of the lesion (cases no. 5, 8, 17, 19, 22, 23, 28, 31, and 36). High means monolateral uptake coincident with the side of the mass. Absent means "cold" lesion.

Abbreviations: N, normal; L, low; H, high; S, suppressed; NS, not suppressed; A, absent; Bilat, bilateral; Hypo, hypodense; Hyper, hyperdense; Inhom, inhomogeneous.

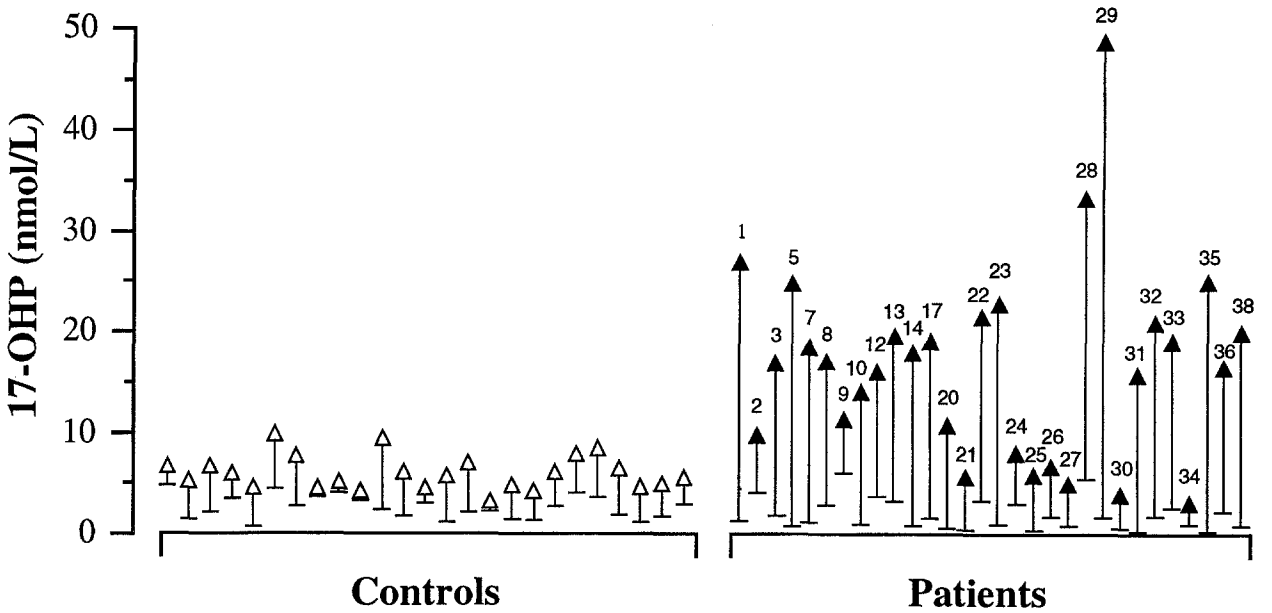

Fig 1. 17-OHP responses (peak value) to ACTH test in 30 patients with incidentaloma (▲) and in normal subjects (△). The basal value (——) represents the mean of values obtained at −15 and 0 minutes.

to the side of the adrenal mass at NP-59 scan. No signs of Cushing's syndrome, virilization, or other abnormalities were present on physical examination.

Patient no. 29, who presented with mild hypertension, refused surgery, and at the 6-month follow-up evaluation, she did not show clinical and/or biochemical signs of progression to overt Cushing's. Cases no. 32 and 38 were submitted to surgery (histologic diagnosis, adrenocortical adenoma). After adrenalectomy, they required glucocorticoid therapy for 1 month. Six months after surgery, the HPA axis was found to be normal. However, DHEA-S levels remained lower than normal. In these patients, the ACTH test showed a normalization of the 17-OHP response in comparison to that observed in the presurgical period (Fig 2).

Patient no. 33 displayed elevated UFC, normal basal levels of serum C with loss of diurnal-rhythm secretion and nonsuppressibility after high-dose DEX, and low basal levels of ACTH with no response to oCRH (Table 1). The adrenal NP-59 scan failed to show any uptake by the adrenal glands. A mild moon-face appearance, mild hypertension, diffuse obesity, and modest edema were clinically identified retrospectively. The patient underwent left adrenalectomy, and an adrenal carcinoma was found. After surgery, she required glucocorticoid therapy; 3 months later, she presented with liver and peritoneal metastases and was treated with mitotane, but she died in 3 months.

CT-guided fine-needle aspiration (FNA) was only performed in two patients, who had adrenal masses with a diameter greater than 3 cm and CT-inhomogeneous enhancement after IV contrast. The cytologic diagnosis (Table 1) was inconclusive in one patient (case no. 8) and adrenal hyperplasia in the other (case no. 22).

Thirteen patients underwent surgical removal (six laparoscopically) of the adrenal masses. Histologic diagnoses are listed in Table 1.

Endocrine evaluation of 6 months after surgery in patients

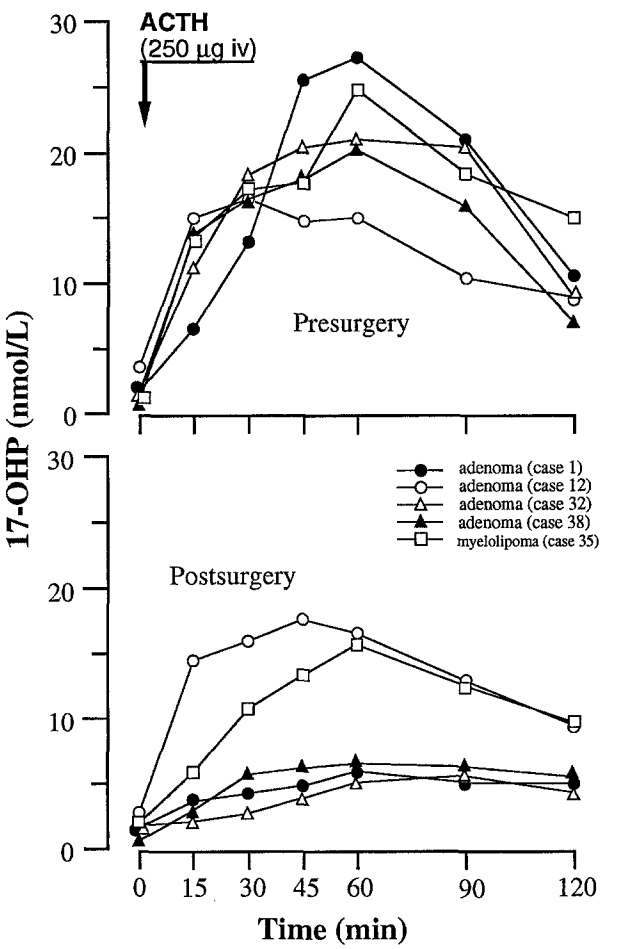

Fig 2. 17-OHP response to ACTH test in 5 patients with adrenal incidentalomas before and after surgery. The value at 0 minutes represents the mean of values obtained at −15 and 0 minutes.

with a histologic diagnosis of nonfunctioning adrenocortical adenoma did not reveal abnormalities in HPA axis function or significant changes in DHEA-S levels compared with presurgical values. Normalization of the abnormal response of 17-OHP to the ACTH test was found after surgery in one patient (case no. 1), but not in the other one (case no. 12) (Fig 2).

Six months after surgery, the patient with myelolipoma (case no. 35) showed a lower response of 17-OHP to ACTH (peak, 15.70 nmol/L at 60 minutes) than that previously observed (peak, 24.85 nmol/L at 60 minutes), although it was still high compared with levels in normal subjects. No changes were observed for the presurgical low levels of DHEA-S.

The 6-month follow-up evaluation in unoperated patients did not reveal any changes either in mass size or in hormonal data. At the 18-month follow-up study, we found an increase in tumor diameter (from 2.5 to 3.5 cm) only in one patient (case no. 30), with no changes in clinical and hormonal data. The patient therefore underwent surgery, and an adrenal hemorrhage was found.

DISCUSSION

The clinical relevance of adrenal incidentalomas depends on the pathology: they may be malignant and/or functional tumors, or they may be masses not requiring resection. Primary adrenal carcinoma is a rare condition, with an annual incidence estimated to range from 0.06 to 0.27 per 100,000 population.[3,10,18] Metastatic lesions are also extremely uncommon in the absence of an obvious primary lesion.[10,12] Indeed, only one patient with adrenal carcinoma was detected in our study. There is evidence that the risk of malignancy for an incidentaloma is correlated to its size. Adrenal masses exceeding 6 cm in diameter may be suspected as carcinoma.[3,10,11] Otherwise, other investigators indicate that all nonfunctioning lesions larger than 3,[2,19] 4,[20] or 5[12] cm should be removed, and that masses smaller than 3 cm are usually benign and can be evaluated prospectively by CT scans at intervals of 2, 6, and 18 months, in accordance with an estimated doubling time for adrenocortical carcinomas.[21] CT images of intratumoral necrosis or hemorrhage, irregular margins, inhomogeneous enhancement after IV contrast, local invasion, and/or absent uptake to NP-59 scan are considered criteria for a high-risk of malignancy.[16] In our series, the largest adrenal mass (12 cm), with radiologic characteristics of malignancy, was found in a patient (case no. 33) with features of a preclinical Cushing's syndrome and histologic diagnosis of adrenal carcinoma. The 10-cm mass (case no. 37) was a pheochromocytoma, which presented a CT picture of inhomogeneous density with areas of necrosis and calcification but regular rounded margins and significant enhancement after IV contrast. The 8-cm myelolipoma (case no. 35) showed a fat density at CT typical for this lesion.[16] Therefore, the imaging characteristics may be potentially decisive factors in the management of adrenal incidentalomas.

NP-59 accumulation achieved by the adrenal cortex has been reported to be a predictor of benignity, while discordant imaging may suggest a malignant lesion.

Gross et al,[22] evaluating 229 nonfunctioning adrenal incidentalomas, showed that NP-59 scintigraphy may have a sensitivity of 71%, specificity of 100%, accuracy of 93%, predictive value of a negative test of 91% (concordant and nonlateralizing scans), and predictive value of a positive test of 100% (discordant scan). In our study, NP-59 scan did not provide unequivocal functional and anatomic information. Absent uptake to the side of the mass was seen in four lesions (cases no. 6, 16, 33, and 35), which were found to be a lymphangiomatous cyst, a myelolipoma, an adrenal carcinoma, and a ganglioneuroma, respectively. In the patient with a left-adrenal C-secreting carcinoma (case no. 33), there was no adrenal NP-59 uptake by the left carcinoma, and the decreased activity of the right adrenal cortex was probably due to suppressed pituitary ACTH release. Since an absence of NP-59 uptake into the adrenal mass may suggest a hypofunctional or space-occupying lesion,[22,23] the discordance between CT scanning and NP-59 scintigraphy (absent or reduced NP-59 accumulation achieved by the abnormal adrenal seen with CT) could be used to determine which patients should undergo surgery. The histologically proven adenomas, either functioning or nonfunctioning, show a monolateral uptake of NP-59 coincident with the side of the adrenal mass, suggesting a degree of relative hyperfunction or autonomy by the lesion. The natural history of "warm" or "hot" adrenal masses in relation to hormonal activity is not clearly understood,[23,24] and an optimal follow-up schedule for these patients is yet to be defined. In conclusion, our data seem to indicate that NP-59 uptake may be useful to characterize the function of the adrenal cortical lesion, whereas more rigorous study is still necessary to define whether this noninvasive test may provide an accurate means to separate benign lesions from malignant lesions.

We discovered two cases of clinically silent pheochromocytoma, with an incidence of 5.3%. This is in accordance with the data reported in the literature[8,11] and confirms the importance of UCA measurement in patients with incidentalomas. Stimulation or suppression tests may be helpful in revealing the presence of subclinical pheochromocytoma, as documented in case no. 15. MIBG scan may add important information, with a sensitivity of 88% for pheochromocytoma and 100% for ganglioneuroma.[24]

C-producing tumors (two adenomas and one carcinoma) were found in three patients (cases no. 32, 38, and 33) exhibiting features of the so-called Cushing's syndrome. Our data are in agreement with recent studies.[5-7] One patient (case no. 29) with a hormonal pattern of preclinical Cushing's syndrome refused surgery and remained completely asymptomatic without clinical or biochemical signs of evolution toward an active Cushing's syndrome at 6 and 12 months of follow-up study. It is well known that the preclinical syndrome does not necessarily evolve toward an overt Cushing's syndrome.[25] However, some cases have been shown to present an evolution in the long run.[26] ACTH and C response to oCRH were impaired in three (cases no. 28, 32, and 33) of four patients with pre-Cushing's, suggesting the suppression of the pituitary adrenal axis. These results may be explained by the different degree and duration of C secretion by individual tumors. Altogether, our data are in agreement with the concept that a lack of C suppressibility by DEX is a sensitive index of the presence of subclinical hypercortisolism, whereas the CRF test may be a useful but nonspecific procedure to evaluate pituitary suppression.[6,27] In these cases, the NP-59 scan has proved a good method for detecting and delineating the functional status

of the mass and the contralateral adrenal suppression, as previously reported.[28]

An exaggerated 17-OHP increase after ACTH was found in 19 patients (63%). This result is in agreement with the reported cases in other series,[14,27,29,30] and may suggest the presence of an asymptomatic 21-hydroxylase deficiency.[17] At the moment, it is still debatable as to whether the enzymatic defect is independent of the adrenal mass, as suggested by the persistence of an increased response of 17-OHP to ACTH in one patient (case no. 2) after monolateral adrenalectomy, or whether it is related and restricted to the tumoral tissue, as indicated by the finding of normalization of 17-OHP after surgical removal of the adrenocortical adenoma in three patients (cases no. 1, 32, and 38). The latter view is corroborated by the recent in vitro study by Racz et al[31] showing lower expression of 21-hydroxylase mRNA and higher 17-OHP content in nonfunctioning cortical adenomas compared with other tissues. However, adrenal masses, including myelolipomas,[32] frequently develop in subjects with congenital adrenal hyperplasia, with an incidence of 82% in homozygotes and 45% in heterozygotes.[13] Our finding of a slight postsurgery reduction in the 17-OHP response to ACTH in the patient bearing a myelolipoma (case no. 35) indicates that the enzymatic deficiency is intrinsic to cortical cells and not specifically restricted to tumoral cells.

Lower than normal serum DHEA-S levels were found in 18 of 38 patients (47%) with adrenal incidentaloma, and they remained abnormally low after ACTH stimulation. This finding is in keeping with previous studies,[20,27,29,33] and might be related to some degree of suppression of normal adrenocortical tissue as a consequence of the negative feedback exerted on ACTH secretion by an autonomously functioning mass. Accordingly, low levels of DHEA-S were recorded in patients with a cortisol-producing tumor (cases no. 32, 33, and 38) and in five patients (cases no. 1, 3, 13, 14, and 29) in whom NP-59 scan showed asymmetrically increased or lateralizing accumulations of radioactivity to the side of the adrenal mass, suggestive of silent hypercortisolism. Of relevance in this context is the finding that DHEA-S remains suppressed for a long period after removal of the adrenocortical adenoma in patients with Cushing's syndrome, ever after recovery of ACTH secretion.[34,35] The presence of a decreased stimulatory activity of ACTH induced by a C-producing adrenal tumor may explain the observation of normal DHEA-S levels in the patient with adrenal carcinoma (case no. 33), unlike that found in these patients in whom DHEA-S is usually elevated.[20,33] Our data indicate that the detection of low DHEA-S concentrations may suggest an alteration in adrenocortical function.

In conclusion, our study confirms that the determination of biochemical activity is a fundamental consideration in the assessment of incidentally discovered adrenal masses, since there are a significant number of patients without evident symptoms or signs of adrenal disease that have subtle alterations of adrenocortical and medullary function. From a clinical point of view, the observation that patients with incidentally discovered adrenal masses frequently showed a decrease in serum levels of DHEA-S suggests that this parameter could be useful for delineating the functional status of the adrenal mass, information not always available by other noninvasive tests.

Measurement of 24-hour UFC and UCA levels, basal plasma levels of adrenocortical hormones, serum electrolyte levels, and DEX suppression must be performed in all patients bearing adrenal incidentaloma. Functional scintigraphy and CT scan can be used to characterize many adrenal masses and to exclude the presence of malignant and/or functioning lesions. Surgery should be reserved for all functioning and nonfunctioning masses greater than 4 cm, even if malignant tumors have been described in smaller (2.5 cm in diameter) incidentally discovered adrenal masses.[24] In this context, detection of radiologic characteristics of malignancy are decisive for surgical treatment. However, different presumptive criteria for the presence of malignancy may be assumed with future experience.

Biochemical and radiologic assessment should be repeated in unoperated patients at 6 and 18 months, in accordance with an estimated doubling time for adrenocortical carcinomas.[21] Moreover, our data indicate that some patients bearing incidentaloma may have an asymptomatic deficiency of 21-hydroxylase activity, and an ACTH test may be indicated to reveal this enzymatic defect. Further in vitro studies are therefore required to define adrenal steroidogenesis in patients with incidentally discovered adrenal masses.

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