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ORIGINAL ARTICLE

Adrenal incidentaloma, clinical, metabolic, follow-up aspects: single centre experience

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Abstract To investigate clinical characteristics, metabolic parameters and follow-up findings of subjects with incidentally discovered adrenal tumors. 376 consecutive subjects who have been evaluated since 2002 were included. Initial radiological examination was CT. Hormonal evaluation included 8.00 a.m. cortisol, DHEA-S, ACTH and in hypertensive subjects, plasma renin activity, and serum aldosterone. Urinary free cortisol (UFC), urinary normetanephrine, and metanephrine were measured. Overnight 1 mg dexamethasone suppression test was performed. Radiological evaluation was performed at 6th and 12th months and annually in subsequent visits. Hormonal evaluation was performed 6 months after the initial visit and annually in subsequent visits. Additionally, patients were evaluated for the development of Type 2 diabetes mellitus, hypertension, hyperlipidemia, and metabolic syndrome in 6-month intervals. Mean age of the participants was 54.7 ± 13.1. Female subjects were more commonly affected (70%). CT was the most frequent radiological intervention that discovered adrenal masses (57%). The vast majority of the participants (85.6%) had benign adrenal adenomas. Primary adrenocortical malignancy was detected in 4 subjects (1.1%). Subjects with adrenal adenomas had significantly smaller tumor diameters ($P \leq 0.001$ vs. other tumors). Sensitivity and specificity of 40 mm as a cut-off value in the differentiation of adrenal gland malignancies from benign tumors was 73.3 and 54.8%, respectively. Most of the adrenal adenomas were non-functioning (73.5%). Subclinical Cushing syndrome (sCS) was detected in 12.5%. The overall prevalence of Type 2 diabetes mellitus, hypertension, hyperlipidemia, and metabolic syndrome was 18.4, 54.9, 59.6, and 48.1%, respectively. They were significantly more common in middle-aged and elderly subjects. During 24 months follow-up 10.2% of adenomas featured increase in tumor diameter and 2.06% developed sCS. Young subjects featured more stable tumor diameter and hormonal status. Most of the incidentally discovered adrenal tumors were non-functioning adrenal adenomas. Clinically overt hormone hypersecretion syndromes were mainly shown in young subjects, while adrenal gland malignancies and sCS were more common in older ages. Mass enlargement and development of subclinical cortisol secretion were not rare and observed especially in middle-aged and elderly subjects. Metabolic derangements were common; however, a possible independent association between adrenal adenoma and metabolic problems need to be elucidated with prospective studies.

Keywords Adrenal · Incidentaloma · Follow-up

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Introduction

Adrenal incidentaloma refers to adrenal tumors, generally with 10 mm or larger diameter, discovered in radiological interventions for indications other than adrenal diseases. Because of the improvements in radiological techniques more people have been diagnosed with adrenal tumors in recent years. However, radiological improvement may not

be the sole factor as the prevalence of adrenal tumors in autopsy series is high suggesting that aging could also be associated with the development of adrenal tumors [1].

The discovery of an adrenal incidentaloma renders the exclusion of malignancy and autonomous hormone secretion. Diagnostic work-up may vary according to different protocols but exclusion of primary or secondary adrenal malignancies or clinically overt hypersecretion syndromes is of vital importance. The understanding of subtle cortisol autonomy (subclinical Cushing Syndrome) and the increased risk of cardiovascular disturbances in those subjects have led to the improvements in diagnostic approach [2].

In this retrospective study we sought to investigate the clinical characteristics, tumor nature, and hormonal status in subjects with incidentally discovered adrenal tumors. We also evaluated the prevalence of several metabolic derangements in participants with adrenal adenomas. Additionally, in a subgroup of subjects with adrenal adenomas, we investigated tumor growth and hormonal status during a median duration of 24 months.

Materials and methods

This retrospective study was conducted in Dokuz Eylul University, Division of Endocrinology. Data of subjects who were referred to our institute with incidentally discovered adrenal tumors since 2002 was evaluated. All referred subjects were recommended radiological, hormonal and metabolic evaluation, and prospective follow-up.

Initial radiological examination was computed tomography (CT) in all subjects. We did not rely on ultrasonographic findings and confirmed the diagnosis with further radiological interventions. Malignancy was excluded if the following criteria were met in CT; (i) regular shape with well-defined margins and homogenous (ii) attenuation value of 10 or less Hounsfield units on unenhanced CT scan, and (iii) 30 or less Hounsfield units on enhanced CT scan. Magnetic resonance imaging (MRI) was performed when CT scan failed to confirm the diagnosis. Additionally, MRI was preferred in cases of hypersensitivity history to non-ionic iodinated contrast medium or history of impaired renal function.

Hormonal evaluation included 8.00 a.m. cortisol, dehydroepiandrosterone sulfate (DHEA-S), adrenocorticotrophic hormone (ACTH) and in hypertensive subjects plasma renin activity and serum aldosterone. Subsequently, urinary free cortisol (UFC) (normal range <110 μg), urinary normetanephrine (normal range: 88–444 μg/day), and urinary metanephrine (normal range: 52–341 μg/day) were measured and overnight 1 mg dexamethasone suppression test (DST) was performed.

The suppression in overnight DST was adequate when morning cortisol fell below 1.8 μg/dl. When post DST cortisol was over 1.8 μg/dl, 2-day 2 mg DST involving the administration of 0.5 mg oral dexamethasone given every 6 h for 48 h was performed. Cortisol autonomy was excluded when post DST cortisol was below 1.8 μg/dl. In subjects with non-suppressed cortisol levels, diurnal rhythm of cortisol was also evaluated (normal: midnight cortisol <7.5 μg/dl). Subclinical Cushing syndrome (sCS) was defined in subjects with adrenal adenomas, in the absence of Cushing syndrome characteristics, when post DST cortisol >1.8 μg/dl and at least one of the following conditions were positive; ACTH < 5 pg/ml, UFC > 110 μg/day, or midnight cortisol >7.5 μg/dl.

Pheochromocytoma was defined with elevated levels of urinary normetanephrine and/or metanephrine. Primary hyperaldosteronism was screened in hypertensive subjects with aldosterone/plasma renin activity ratio (ARR). In subjects with ARR >25, saline infusion test was performed. Adrenal vein sampling was performed in 1 subject.

Adrenalectomy was recommended in case of development of overt hormone hypersecretion, significant mass enlargement or radiological suspicion of adrenal malignancy.

In subjects whom were suggested follow-up, radiological evaluation was performed with CT and/or MRI at 6th and 12th months and annually in subsequent visits. Increase in tumor diameter was defined as the change of diameter from baseline measure. Hormonal evaluation was performed 6 months after the initial visit and annually in subsequent visits. Among 293 subjects with adrenal adenomas, prospective follow-up data regarding tumor diameter and hormonal status was achieved for 162 individuals. Additionally, patients were evaluated for the development of Type 2 diabetes mellitus, hypertension, hyperlipidemia, and metabolic syndrome in 6 month intervals.

Type 2 diabetes was diagnosed if the subject had a prior diagnosis or has been on diabetes medications. In subjects without diabetes, diagnosis was established according to the diagnostic criteria of American Diabetes Association [3]. Hypertension was diagnosed if the subject had a prior diagnosis or has been on anti-hypertensive medications. In subjects without hypertension, diagnosis was established if systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg. Hyperlipidemia was diagnosed in the presence of a prior diagnosis or use of anti-hyperlipidemic medications. In subjects without hyperlipidemia, diagnosis was established if total cholesterol ≥200 mg/dl and LDL-C ≥130 mg/dl or with the presence of isolated hypertriglyceridemia (≥200 mg/dl). Metabolic syndrome was defined if participants had three or more of the following; waist circumference ≥102 cm in men and ≥88 cm in women; serum triglyceride level ≥150 mg/dl; HDL cholesterol <40 mg/dl

in men and <50 mg/dl in women; blood pressure ≥130/85 mm Hg; fasting glucose ≥110 mg/dl [4].

Cortisol, DHEAS, and ACTH were measured using chemiluminescence enzyme immunoassay kits (Immulite, Diagnostic Products Corporation, Los Angeles, USA). Plasma renin activity and aldosterone were measured using radioimmunoassay kits. Urine free cortisol and metanephrines were measured by high performance liquid chromatography (Agilent Technologies, Santa Clara, USA).

Statistical analysis was performed with SPSS V15.0. Variables with normal distribution were expressed as mean ± standardized deviation (SD). Median and range was given for the variables without normal distribution. Comparisons between groups were performed with Chi-square test for dichotomous variables. Continuous variables were assessed by Independent Samples *T*-test, Mann–Whitney U test or one-way ANOVA.

Results

Baseline characteristics

Table 1 demonstrates the baseline characteristics of participants with incidentally discovered adrenal tumors. We evaluated 376 subjects with incidentally discovered adrenal tumors since 2002. Female subjects were more commonly affected (70.7 vs. 29.3%). Mean age of the participants was 54.7 ± 13.1. Sixty-eight percent of the subjects were older than 50 years old.

The leading causes of abdominal imaging were non-specific symptoms (24%), gastrointestinal symptoms (20%), respiratory symptoms (15%), history of extra-adrenal malignancy (11%), and poorly controlled blood pressure (11%).

In our survey, CT was the most frequent radiological intervention that discovered adrenal masses (57%). The lesions detected by ultrasonography were larger than those which were detected by CT or MRI (33.1 ± 16.8 mm, 23.1 ± 10.3 mm, 20.3 ± 10.1 mm, respectively, $P < 0.001$). Ultrasonography detected right sided adrenal tumors more frequently (62 vs. 38%) when compared to CT (43 vs. 57%) and MRI (50 vs. 50%).

In our series, 83.2% ($n = 313$) of the incidentally discovered adrenal tumors were single. Multiple adrenal tumors were discovered in 16.8% of the subjects ($n = 63$). In subjects with multiple adrenal tumors, 54 subjects had bilateral tumors, 5 subjects had multiple left adrenal gland tumors, and 4 subjects had multiple right adrenal gland tumors. Patients with multiple adrenal tumors were significantly older (53.8 ± 13.7 vs. 59.3 ± 8.3, $P < 0.001$). In male subjects the rate of multiple tumors was slightly higher than the rate in females (21.8 vs. 14.6%, $P = 0.097$).

Seventy-six subjects underwent adrenalectomy. The indications for surgery were; pheochromocytoma ($n = 20$),

Table 1 Clinical characteristics of subjects with incidentally discovered adrenal tumors and the variations of baseline parameters in different age groups

	All subjects ($n = 376$)	Group A 18–39 years ($n = 42$)	Group B 40–64 years ($n = 245$)	Group C 65≤ years ($n = 89$)
Gender (F/M ratio)	2.41	4.88	2.33	1.94[±]
Initial imaging (USG/CT/MRI) (%)	34/57/9	52/38/10	34/58/8	25/63/12
Tumor diameter (mm)	25 (7–97)	26 (8–62)	25 (7–97)	20.5 (7–84)[#]
Multiple tumors (%)	16.8	–	18.8	19[#]
Extra-adrenal malignancy (%)	16.2	7.1	16.0	15.7
Non-functioning adenoma (%)	67.4	40.5	68.5	76.4
Subclinical Cushing syndrome[a] (%)	10.9	4.8	10.2	15.7
Cushing syndrome (%)	4.0	16.7	3.3	–
Pheochromocytoma[b] (%)	5.3	14.3	5.7	–
Primary hyperaldosteronism (%)	4.0	7.1	4.9	–
Adrenal cyst (%)	2.7	14.3	1.6	–
Adrenal myelolipoma (%)	2.1	2.4	1.6	3.4
Adrenal metastasis (%)	3.7	–	4.1	4.4

Data was given mean ± SD or median (range)

[±] $P < 0.05$ and [#] $P < 0.01$ A versus C

[a] In subclinical Cushing syndrome group, 1 patient had primary adrenocortical carcinoma

[b] 3 subjects had malignant pheochromocytomas

Cushing syndrome ($n = 15$), Primary hyperaldosteronism ($n = 8$), sCS with metabolic disturbances ($n = 4$), large tumor (>4 cm) or suspicious appearance on radiological interventions ($n = 29$). Histological diagnosis was adenoma ($n = 38$), benign pheochromocytoma ($n = 17$), malignant pheochromocytoma ($n = 3$), primary adrenocortical carcinoma ($n = 1$), adrenal metastasis ($n = 12$), adrenal myelolipoma ($n = 3$), and adrenal cyst ($n = 2$). Patients who underwent adrenalectomy were younger (49.8 ± 14.4 vs. 56.0 ± 12.5, $P < 0.001$) and dominantly male (27% of males and 17% of females had adrenalectomy, $P = 0.034$). They had larger tumor diameters (40 (7–97) vs. 20 (7–65), $P < 0.001$). In our series, sensitivity and specificity of 40 mm as a cut-off value in the differentiation of primary or secondary adrenal gland malignancies from benign adrenal masses was 73.3 and 54.8%, respectively. Additionally, positive and negative predictive values were 28.2 and 89.4%.

Radiological and histological features

Table 2 shows the data regarding the type of the tumors. Radiological and histological data of the participants demonstrated that vast majority of the participants ($n = 322$, 85.6%) had benign adrenal adenomas. Primary adrenocortical malignancy (1 adrenocortical carcinoma, 3 malignant pheochromocytomas) was detected in 4 subjects (1.1%). Adrenal metastasis was shown in 14 (3.7%) subjects. The primary malignancy sites were lung cancer ($n = 8$), renal cell carcinoma ($n = 3$), non-Hodgkin lymphoma ($n = 2$), and pancreas carcinoma ($n = 1$). Benign pheochromocytomas were found in 17 subjects (4.5%). There were 11 patients with adrenal cysts (3%) and 8 subjects with adrenal myelolipomas (2.1%). Patients with benign pheochromocytomas and adrenal cysts were significantly younger than subjects with other tumors. Adrenal adenomas, adrenal cysts, and myelolipomas were significantly more common in females when compared to male subjects. Rate of benign pheochromocytomas and primary adrenocortical malignancies was similar between females and males while adrenal metastasis was significantly more common in male patients. Tumor diameter was found to be significantly small in subjects with adenomas when compared to patients with other tumor types.

Hormonal features

Table 3 shows the characteristics of participants with adrenal adenomas regarding the hormonal evaluation. After the exclusion of subjects with adrenal metastasis, adrenal

Table 2 Radiological and histological data of subjects with incidentally discovered adrenal tumors

	No (n, %)	Age	Female/male	Diameter (mm)
Adrenal adenoma	322 (85.6)	55.5 ± 12.6	2.9	20 (7–60)
Primary adrenal malignancy[a]	4 (1.1)	62.2 ± 4.9	1.0	82 (70–90)‡
Benign pheochromocytoma	17 (4.5)	$44.9 \pm 12.4^{\dagger}$	1.1	50 (25–97)‡
Adrenal cyst	11 (3.0)	$37.4 \pm 16.5^{\ddagger}$	2.6	30 (24–62)‡
Adrenal myelolipoma	8 (2.1)	55.0 ± 16.7	1.6	45 (20–70)‡
Adrenal metastasis	14 (3.7)	61.1 ± 9.9	0.07	40 (10–70)‡

Data was given mean ± SD or median (range)

Histological data was present for 76 subjects who underwent adrenalectomy

‡ $P \leq 0.001$, † $P < 0.01$ versus adrenal adenoma

[a] There was 1 subject with primary adrenocortical carcinoma and 3 subjects with malign pheochromocytomas

Table 3 Hormonal evaluation data of subjects with incidentally discovered adrenal tumors after the exclusion of metastasis, cysts, and myelolipomas ($n = 343$)

	No (n, %)	Age	Female/male	Diameter (mm)
Non-functioning adenoma	252 (73.5)	56.0 ± 12.3	2.7	20 (7–60)
Subclinical Cushing syndrome	41 (12.0)	58.8 ± 10.5	4.1	29 (10–84)‡
Pheochromocytoma	20 (5.9)	$47.2 \pm 12.8^{\dagger}$	1.0	50 (25–97)‡
Cushing syndrome	15 (4.4)	$40.1 \pm 12.4^{\ddagger}$	14.0	35 (20–60)‡
Primary hyperaldosteronism	15 (4.4)	$49.1 \pm 11.5^{\#}$	2.7	14 (7–20)‡

Data was given mean ± SD or median (range)

‡ $P < 0.001$, † $P < 0.01$, $^{\#}$ $P = 0.057$ versus non-functioning adenoma

Table 4 Metabolic characteristics of subjects with non-functioning adrenal adenomas and subclinical Cushing syndrome

	All subjects ($n = 293$)	Group A 18–39 years ($n = 19$)	Group B 40–64 years ($n = 193$)	Group C 65≤ years ($n = 81$)
Metabolic syndrome (%)	48.1	23.5	47.7	54.9
Type 2 diabetes (%)	18.4	5.3	13.1	33.8
Hypertension (%)	54.9	16.7	49.2	77.6
Hyperlipidemia (%)	59.6	47.4	64.2	51.9

Table 5 Prospective evaluation of adrenal adenomas in age groups

	Group A 18–39 years ($n = 11$)	Group B 40–64 years ($n = 108$)	Group C 65≤ years ($n = 43$)
Follow-up duration (months)	24 (7–103)	23 (6–100)	25 (6–132)
Increase ≥10 mm in diameter (n, %)	1 (9.1)	5 (4.6)	4 (9.3)
Increase <10 mm in diameter (n, %)	–	18 (16.6)	2 (4.6)
Decrease in diameter (n, %)	–	5 (4.6)	3 (6.9)
Development of Cushing Syndrome (n, %)	–	–	–
Development of subclinical CS (n, %)	–	5 (4.6)	1 (2.3)
Development of pheochromocytoma (n, %)	–	–	–
Development of PHA (n, %)	–	–	–

Please note that the table demonstrates follow-up data of subjects with adrenal adenomas but not other tumor types

cysts, and adrenal myelolipomas there were 343 subjects whom were evaluated for the hormonal status of the adrenal mass. In this group, the majority of the subjects had non-functioning adrenal adenomas ($n = 252$, 73.5%). There were 15 (4.4%) subjects with Cushing syndrome, 15 subjects with primary hyperaldosteronism (4.4%), 20 subjects with pheochromocytomas (5.9%), and 41 subjects with sCS (12.0%). Subjects with clinically overt hormone hypersecretion were significantly younger than subjects with non-functioning adenomas and subjects with sCS. Female dominance was not significant only in subjects with pheochromocytomas. Subjects with subclinical or overt hormone hypersecretion featured significantly larger tumors when compared to non-functioning adenomas except participants with primary hyperaldosteronism who had the smallest median tumor diameter.

In 41 subjects with elevated post DST cortisol and sCS the rate of other hormonal abnormalities were as follows; disturbed diurnal rhythm (66%), suppressed ACTH (62.5%), suppressed DHEAS (57.1%), and high UFC (50.0%). Morning cortisol level was also significantly higher than subjects with non-functioning adrenal adenomas (17.5 ± 5.4 vs. 14.2 ± 5.8 μg/dl, $P < 0.001$).

Metabolic findings

Metabolic features of participants were evaluated in subjects with non-functioning adrenal adenomas and sCS ($n = 293$). Table 4 demonstrates the prevalence of several metabolic disturbances. The prevalence of Type 2 diabetes mellitus, hypertension, hyperlipidemia, and metabolic syndrome was 18.4, 54.9, 59.6, and 48.1%, respectively. Middle-aged and elderly subjects with adrenal adenomas featured increased prevalence of metabolic derangements when compared to young participants.

Follow-up findings

Among 293 subjects with non-functioning adrenal adenomas and sCS, we had prospective data regarding tumor diameter and hormonal status evaluation in 162 subjects. Table 5 demonstrates the follow-up data in terms of age groups. During a median follow-up duration of 24 months, increase in tumor diameter was observed in 30 cases (10.2%) and decrease in tumor diameter was observed in 8 cases (2.7%) cases. Development of clinically overt hormone hypersecretion was not observed while 6 cases (2.06%) developed sCS. Young subjects featured more stable tumor diameter and hormonal status when compared to middle-aged and elderly participants.

Discussion

The largest clinical series of adrenal incidentalomas which evaluated 1004 subjects form 26 centers in Italy was

reported by Mantero et al. [5] 10 years ago. Detailed evaluation of large series has been lacking so far. In this present study, we evaluated several aspects of adrenal incidentalomas including clinical characteristics, tumor nature, hormonal status, metabolic parameters, and follow-up data in a cohort of 376 participants.

In our series, we observed that incidentally discovered adrenal tumors were more common in middle-aged and elderly subjects. Autopsy series in elderly subjects demonstrated that the true prevalence of asymptomatic adrenal tumors was higher than that achieved from CT series [1]. Previous studies have demonstrated that cortical cells featured compensatory hyperplasia as a response to aging related ischemia and atrophy [6]. This observation and the increased number of radiological procedures could explain the increased frequency in the elderly.

In this study the initial imaging intervention was CT in 57% of the participants. Interestingly, Mantero et al. [5] reported that 70% of the adrenal lesions in their survey were detected by ultrasonography. This variation may demonstrate the change in surveillance attitudes of asymptomatic people during a decade. Ultrasonography detected adrenal masses were significantly larger than did CT and MRI. This may be associated with the higher rate of ultrasonographic imaging in young individuals in whom clinically overt hormone hypersecretion and naturally larger tumors were commonly detected. Furthermore, the detection of smaller adrenal lesions in CT and MRI were reported to be more effective than ultrasonography [7].

Adrenalectomy was suggested to 76 patients in our series. The leading cause of surgery was the clinically overt hormone hypersecretion syndromes ($n = 43$, 56.5%). We defined 1 subject with primary adrenocortical carcinoma in the series. She was a 68-year-old female with a rapidly growing adrenal mass; from 25 to 85 mm in 6 months. Current guidelines regarding management of adrenal lesions suggest diameter as one of the most important factors for the prediction of tumor's nature. It has been shown that the risk of malignancy increased significantly in lesions larger than 40 mm [8, 9]. In our series, sensitivity and specificity of 40 mm was 73.3 and 54.8%, respectively. Additionally, positive and negative predictive values were 28.2 and 89.4%. Mantero et al. [5] in their survey showed that sensitivity and specificity of 40 mm were 93 and 42%. Their exclusion of adrenal metastasis might explain the difference between results because, in our survey, 28.5% (4/14) of subjects with adrenal gland metastasis presented with lesions <40 mm. In any case, negative predictive value of 40 mm is a reliable standard and should be considered along with the other radiological features. Mantero et al. [5] in their multicentre survey defined 47 subjects with carcinomas and 7 subjects with metastasis among 1004 participants and found an overall prevalence of 5.8%. In our series the cumulative prevalence of adrenal gland malignancies (primary + metastasis) was 4.8%. Our findings and previous data demonstrate that adrenal gland malignancies are not quite rare. We suggest that radiological monitoring, especially for subjects with larger tumors, is mandatory.

Our data showed that vast majority of the adrenal incidentalomas were non-functioning adenomas. The most frequent hormonal disturbance was sCS. sCS has been defined as the subtle cortisol autonomy of an adrenal adenoma which does not cause clinically overt hypercortisolism but can be shown by laboratory investigations [10]. Because of the lack of certain diagnostic criteria, reported prevalence rates have shown diversity. In our series, we accepted a participant as sCS if he or she had non-suppressed post DST cortisol and at least one additional abnormal HPA axis test. Among HPA axis tests disturbed diurnal rhythm of cortisol was the most common abnormal test (66%) when compared to suppressed ACTH level (62.5%), suppressed DHEAS (57.1%), and elevated UFC (50.0%). The loss of the diurnal rhythm of cortisol secretion and the increase in midnight cortisol level has been suggested as the earliest deteriorations in subjects with endogenous hypercortisolism [10].

In the last decade several authors have addressed the question whether adrenal adenoma could be associated with metabolic problems and poor cardiovascular outcome. Subtle cortisol autonomy of adrenal adenoma has been suggested to have a role in the development of metabolic derangements [1, 11–14]. In our series, we demonstrated significantly higher prevalence rates of metabolic syndrome, Type 2 diabetes, hypertension, and hyperlipidemia in participants with non-functioning adrenal adenomas and sCS. However, distribution of the disturbances in age groups has yielded the role of aging in the development of unfavorable metabolic outcome. In young subjects the prevalence rates of metabolic syndrome, Type 2 diabetes and hypertension were lower than the rates in general Turkish population. In middle-aged and elderly subjects prevalence rates were apparently high. Our current knowledge is not sufficient for a clear explanation for these findings especially for subjects with non-functioning adrenal adenomas. First, the increase in metabolic problems may be solely related with aging but not with adrenal adenoma because, in our series, young subjects were not affected as middle-aged and elderly subjects did. Nevertheless, considering a possible link between adrenal adenoma and unfavorable metabolic status, we may suggest that the shorter duration of exposure to cortisol autonomy might be responsible for the lower prevalence rates of metabolic deteriorations in young subjects. Alternatively, it can also be suggested that insulin resistance and hyperinsulinemia could be associated with the development of

adrenal adenomas via mitogenic pathways. Therefore, more evidence is needed to support one of these hypotheses.

Prospective evaluation of a subgroup of 162 subjects with adrenal adenomas yielded stable tumor size and hormonal status in young subjects. Despite similar follow-up duration, middle-aged and elderly participants featured apparently more frequent development of sCS or changes in adenoma diameter. It was previously demonstrated that adrenocortical morphology revealed an age-related reduction in the thickness of the adrenal cortex and an increase of microhemorrhagic events [15, 16]. This has been suggested as the underlying cause of the age-dependent high frequency of adrenal nodules and for our study, could explain the increased frequency of tumor diameter variations in middle-aged and elderly subjects. Additionally, in middle-aged and elderly subjects significant alterations of HPA axis such as increased morning and midnight cortisol levels were demonstrated previously [17, 18]. This previous data could explain both the increased prevalence of sCS in middle-aged and elderly subjects at diagnosis and also could be associated with the considerable tendency to develop sCS in this group during follow-up.

In summary, adrenal incidentalomas were more frequently detected in middle-aged and elderly subjects. Vast majority of the incidentalomas was non-functioning adenomas. Tumor growth and development of sCS were significantly frequent in middle-aged and elderly subjects. Metabolic problems frequently accompanied adrenal adenomas. However, whether poor metabolic outcome was independently associated with adrenal adenoma or those metabolic deteriorations were consequences of aging need to be elucidated with prospective studies.

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