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Clinical characteristics and follow-up of incidentally found adrenal tumours - results from a single tertiary centre

Research Article

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Abstract: Aim: To evaluate the clinical features, hormonal activity and natural evolution of adrenal incidentalomas (AI) in patients investigated in a single endocrinological centre and compare the prevalence of metabolic disorders and hypertension between subjects with AI and the general population. Patients and methods: 515 patients with AI evaluated between 1995 and 2010 were retrospectively included in the study. Their anthropometric, clinical, metabolic and hormonal parameters were analyzed. Follow-up data was available for 142 patients. Results: Mean age of all participants was 53.45 ± 13.4 years (range 13 – 84) with strong female predominance – 376 (73%) vs. 139 (27%) males. Median size of AI was 28 mm (range 10 – 190 mm). Hormonal investigations revealed that 82.9% of patients harboured non-functioning adenomas, subclinical hypercortisolism was detected in 5.94%, overt Cushing's syndrome – in 2.7%, pheochromocytoma – in 1.9% and primary aldosteronism was diagnosed in 1% of patients. Adrenal carcinoma was identified in 1.7%. The prevalence of metabolic abnormalities and hypertension did not differ between patients with subclinical Cushing's syndrome and non-functioning adrenal adenomas. When compared to the general population, however hypertension, type 2 diabetes and metabolic syndrome were significantly more common in patients with hormonally inactive tumours. During the course of follow-up progression to overt hormonal hypersecretion was not observed. Conclusion: These results confirm other contemporary studies reporting lower rates of hormonally active and malignant lesions among AI as well as increased prevalence of hypertension and metabolic abnormalities in patients with non-functioning adrenal adenomas.

Keywords: *Adrenal incidentaloma • Cushing's syndrome • Pheochromocytoma • Primary aldosteronism*

1. Introduction

Adrenal tumours constitute a heterogeneous group of neoplasms with diverse functional characteristics and evolution whose growing recognition in recent years exerts an increasing pressure on medical specialists and health care systems. In the last 25 years a large number of them are discovered by chance as a by-product of modern imaging techniques and are termed "incidentalomas". The definition of adrenal incidentaloma includes any adrenal mass over 1 cm in diameter that is unexpectedly revealed in the course of diagnostic or therapeutic procedures undertaken for reasons unrelated to any clinical suspicion of adrenal dysfunction. Analyses of published autopsy series indicate prevalence of adrenal incidentalomas from 2.3% to 6% in the general population with age being the most important determinant: they are found in less than 1% in subjects < 30 years compared to almost 7% in individuals older than 70 years [1,2]. Prevalence data from abdominal and chest CT studies started from 0.35% in the 1980s and increased up to 4.4% with the wide-spread introduction of modern high-resolution scanners in recent years, approximating the percentage from autopsy series [3-6]. A wide range of pathologies such as primary or metastatic malignancies, pheochromocytoma, cortisol- or aldosterone-secreting adenomas may present as adrenal incidentalomas but the majority are benign adrenocortical adenomas that show no signs of hormonal hypersecretion [7]. The challenge for physicians lies in identifying the tumours that confer a significant health risk for the patient either by their malignant po-

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tential or autonomous hormonal activity. Current consensus statements and guidelines [8-10] recommend surgery as the treatment of choice for such lesions and conservative approach including periodic radiological and hormonal evaluation when managing the benign non-functioning adrenal adenomas. However, long-term data on the natural evolution and potential changes in size and pattern of secretion of these tumours is still scarce. Increasing evidence suggests that even the apparently non-functioning adrenal adenomas may be associated with higher prevalence of hypertension and a variety of metabolic abnormalities such as obesity, diabetes mellitus type 2, impairments of glucose metabolism and dyslipidaemia compared to the general population [11-19]. These derangements are usually explained by subtle autonomous hormonal secretion, mostly of cortisol, that is insufficient to cause the typical clinical manifestations of overt Cushing's syndrome. The condition was therefore termed subclinical Cushing's syndrome (SCS). Its prevalence varies from 5% to almost 50% of all adrenal incidentalomas in the different published series mainly because of lack of unified diagnostic criteria and different reliability of the biochemical assays used [1,12,20-22]. Management of SCS also presents another area of controversy as progression to overt Cushing's syndrome seems to be rare. On the other hand, however, some patients may benefit from regression of the associated cardiovascular and metabolic risk factors after surgery [7,22-25].

The aim of the present study was retrospective analysis of tumour nature, clinical features and hormonal patterns in subjects with incidentally discovered adrenal adenomas that were evaluated in a tertiary endocrinological centre in Bulgaria. We also assessed the prevalence of hypertension and several metabolic disorders among patients with non-functioning adrenal adenomas in comparison to the general Bulgarian population. Finally, we investigated the long-term evolution of tumor size and hormonal activity in the subgroup of patients not indicated for surgery.

2. Patients and methods

After approval from the local Ethical committee data from the medical records of 515 patients evaluated for incidentally discovered adrenal tumours in the Clinical Centre of Endocrinology in Sofia, Bulgaria between 1995 and 2010 were retrospectively reviewed. Criteria for inclusion in the study were unilateral or bilateral lesions clearly originating from the adrenal glands that were detected by computer tomography (CT) or magnetic resonance imaging (MRI) performed for unrelated disorders. Patients with adrenal adenomas discovered initially by ultrasound examination were included only if they had at least one confirmatory CT or MRI scan. Concomitant malignancies and possible metastatic disease were excluded by detailed revision of the medical records, comprehensive review of the radiological scans and lack of alteration in blood tests suggestive of malignant disease such as increased erythrocyte sedimentation rate, hypercalcaemia, leucocytosis, thrombocytosis etc. When assessing tumour size the largest diameter was considered in unilateral adenomas and the largest mass in bilateral lesions.

The investigation protocol employed in our centre included complete history and thorough physical examination with measurement of weight, height, waist circumference, systolic and diastolic blood pressure and calculating body mass index (BMI). Standard biochemical investigation consisted of serum electrolytes, plasma glucose, total and HDL cholesterol, triglycerides, uric acid and creatinine obtained after overnight fasting. Hormonal evaluation included morning (08.00 h) and midnight (24.00 h) serum cortisol, urinary free cortisol (UFC) excretion in 24 h urine, dehydroepiandrosterone sulphate (DHEAS), plasma adrenocorticotropic hormone (ACTH) and urinary cateholamines or metanephrines. In patients with clinical suspicion of hypercortisolism and/or abnormal results from the serum or urinary cortisol measurements 1 mg overnight dexamethasone suppression test was performed. In hypertensive patients blood samples for serum aldosterone and plasma renin activity (PRA) were also collected in a sitting position after discontinuation of all medications known to affect the renin-aldosterone-angiotensin system (RAAS) for at least 10 days. In case of spironolacton treatment the wash-out period was increased to 45 days. During this time patients received alternative antihypertensive therapy with calcium channel blockers and/or central α_2 adrenergic receptor agonists. Patients with elevated aldosterone to PRA ratio underwent captorpril suppression test for confirmation or exclusion of hyperaldosteronism. All biochemical and hormonal investigations were performed in the same laboratory using commercially available assay kits.

A decision for surgical treatment was taken when the adrenal mass was larger than 40 mm or presented with radiological characteristics suspicious for malignancy such as irregular borders and non-homogeneous intratumoral structure taking into account patients' age, preferences and presence of co-morbid conditions. Surgery was also undertaken in cases of overt hormonal hypersecretion and when tumour growth was documented during subsequent follow-up. Classic Cushing's syndrome due to cortisol secreting adenoma was diagnosed when hormonal assessments revealed loss of di-

urnal rhythm of serum cortisol, elevated urinary cortisol excretion, lack of suppression under 50 nmol/L of serum cortisol after 1 mg dexamethasone and suppressed ACTH in patients exhibiting some typical features of corticosteroid excess like central fat predisposition, moon face, purple striae or skin atrophy. Subclinical hypercortisolism was considered when such specific symptoms were absent but the patients could not achieve cortisol suppression below 50 nmol/L after administration of 1 mg dexamethasone combined with at least 1 another abnormal test of the hypothalamic pituitary adrenal (HPA) function. Arterial hypertension, diabetes mellitus type 2 and obesity were not considered to be specific symptoms of hypercortisolism. The diagnosis of pheochromocytoma required the measurement of elevated urinary free metanephrines or urinary cateholamines. Primary hyperaldosteronism caused by aldosterone producing adenoma was diagnosed in hypertensive patients with elevated ALD/PRA ratio and lack of aldosterone suppression after captopril administration. When hormonal hypersecretion was excluded patients with adrenal adenomas smaller than 40 mm and benign radiological features were suggested annual hormonal and imaging re-evaluation.

All patients with adrenal incidentalomas were investigated for presence of co-morbidities and the possible complications of subclinical hypercortisolism both at baseline and at subsequent follow-up. Patients repeatedly having systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg as well as those receiving anti-hypertensive therapy for already established diagnosis were regarded as having arterial hypertension. Obesity was considered when patients presented with BMI grater than 30 kg/m^2. Type 2 diabetes and impairments of glucose metabolism were defined according to WHO criteria [26]: diabetes was diagnosed when fasting plasma glucose was repeatedly above 7 mmol/L and/or levels exceeded 11.1 mmol/L 120 min after oral glucose tolerance test (OGTT) with 75 mg of glucose. Patients with definitive prior diagnosis and receiving hypoglycemic medications were also regarded as diabetic. Dyslipidaemia was present if total cholesterol exceeded 5.2 mmol/L, high-density lipoprotein cholesterol was below 1.0 mmol/L in males and below 1.3 mmol/L in females or triglycerides levels were greater than 1.7 mmol/L [27]. Metabolic syndrome was considered in patients with abdominal obesity defined as waist circumference larger than 94 cm for men and 80 cm for women and the presence of at least two of the following abnormalities: triglycerides >1.7 mmol/L, HDL < 1.0 and <1.3 for men and women respectfully, arterial hypertension, fasting plasma glucose above 5.6 mmol/L or overt diabetes [28].

For the purpose of comparison of the prevalence of hypertension and type 2 diabetes in patients with non-functioning adrenal adenomas and the general Bulgarian population we used data from a recently published large cross-sectional study evaluating the frequency of these conditions among 2415 randomly selected subjects (1348 females and 1067 males) from 28 regions in the country [29,30]. This study was considered broadly representative of the general population.

2.1 Statistical analysis

Calculations were performed using SPSS software package (version 17.0, Chicago, IL, USA). Statistical significance was set at $p<0.05$. Normality of data distribution was assessed by Kolmogorov-Smirnov test. Continuous variables with normal distribution are expressed as mean ± SD. Median and interquartile range are used to describe variables following non-Gaussian distribution. Frequencies of studied parameters are presented as percentages. Categorical variables are compared using χ^2 test or Fisher's exact test. The hypothesis about equality of population means was tested by Student's t-test for two independent samples or Mann-Whitney test depending on the normality of distribution. When medical records did not contain data on a required variable patients were excluded form the particular analysis.

3. Results

After the initial review of the medical records 515 patients were considered eligible for data analysis. Mean age was 53.45 ± 13.4 years (range 13 – 84) and female sex was largely predominant – 376 (73%) vs. 139 (27%) male subjects. Women were also slightly younger at diagnosis – 52.57 ± 13.8 vs. 55.85 ± 12.14 years (p=0.014). The number of patients with adrenal incidentalomas steadily increased from only 5 subjects in 1995 to 69 and 63 patients per year in 2009 and 2010 respectively. Almost 80% of all patients were diagnosed after 2003. The demographic characteristics of patients diagnosed earlier were however no different from the entire series which allowed their inclusion in the overall analysis. Adrenal incidentalomas were most commonly detected in patients in their sixth or seventh decade (Figure 1). The left adrenal gland was more frequently affected – in 266 patients (51.9%), than the right – in 202 patients (39.4%), and 45 patients (8.8%) harbored bilateral lesions. No significant sex differences were observed for the location of the adrenal mass. Median size of the adrenal tumours was 28 mm (range 10 – 190 mm).

Hormonal evaluation revealed overt hypersecretion in 29 patients (5.6%) with adrenal incidentalomas. The

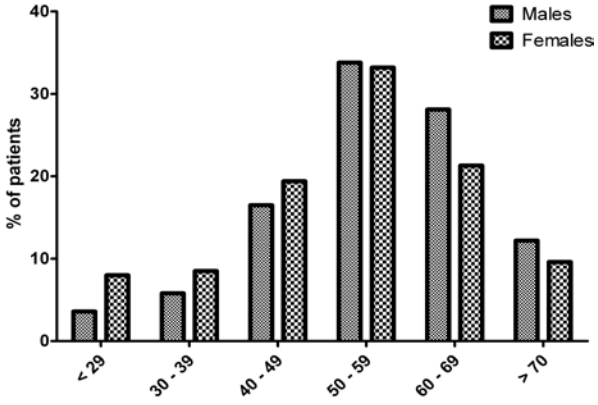

Figure 1. Age and sex distribution of patients with incidentally discovered adrenal adenomas.

most common entity was Cushing's syndrome that was diagnosed in 14 patients (2.7%), pheochromocytoma was revealed in 10 subjects (1.9%) and the adrenal tumour was identified as Conn's adenoma least often - in 5 patients (1%). Adrenal carcinoma was diagnosed in 7 patients (1.3%). Using the adopted criteria for subclinical Cushing's syndrome the condition was identified in 32 patients (5.94%). The remaining 447 patients (82.9%) with adrenal incidentalomas were classified as having non-functioning adrenal adenomas (NFAA). Some demographic, clinical and biochemical features of patients with different types of adrenal tumours are shown in Table 1. Mean age was similar in almost all groups except for the patients with pheochromocytoma who were significantly older than patients with NFAA (p=0.048). Similarly, female subjects outnumbered males in all but one group – that of primary aldosteronism. Concerning tumour size, significant differences were observed between some groups. Patients with adrenal carcinomas harboured the largest tumours - 85 mm [46-63] (p<0.001 compared to patients with NFAA), followed by pheochromocytoma patients – 50 mm [38-57] (p=0.002 compared to NFAA). Cortisol producing adenomas were also larger than NFAA (33 mm [30 - 60] vs 27 mm [17-38], p =0.035). Patients with primary aldosteronism had the smallest tumours but the difference with NFAA was not significant. The proportion of bilateral lesions was significantly higher in patients with subclinical Cushing's syndrome compared to NFAA (21.9% vs 7.8%, p=0.015).

All 5 patients with aldosterone-producing adenoma had hypertension but only two of them presented also with hypokalemia. Two patients with pheochromocytoma (20%) were asymptomatic and had no history of increased arterial pressure: one had neurofibromatosis type 1 and the other had type 2 diabetes. The rest had been hypertensive for various periods but their condition was not suspected until the detection of the adrenal tumour. Surgery was undertaken in all but one female patient with identified pheochromocytoma who was not operated because of advanced age, presence of co-morbidities and adequate control on therapy with α-adrenergic blockers. All patients with Cushing's syndrome experienced unequivocal evidence for autonomous cortisol hypersecretion: lack of suppression after 1 mg dexamethasone, suppressed ACTH, elevated urinary free cortisol and disrupted circadian rhythm. The clinical symptoms of hypercortisolism were also present although less pronounced. Patients most often exhibited abdominal obesity, easy skin bruising, unexplained fatigue and depression. Some patients were diagnosed

Table 1. Demographic and clinical characteristics of patients with different types of incidentally found adrenal tumours.

	All patients (n=515)	Cushing's syndrome (n=14)	Pheochromocytoma (n=10)	Primary aldosteronism (n=5)	Adrenal carcinoma (n=7)	Subclinical Cushing's syndrome (n=32)	Non-functioning adenoma (n=447)
Age, years	53.5 ± 13.4	52.9 ± 7.1	61.9 ± 10.5	53.8 ± 20.2	53.1 ± 10.6	55.1 ± 8.9	53.2 ± 13.9
Sex							
Males (%)	139 (27%)	2 (14%)	2 (20%)	3 (60%)	1 (14%)	8 (25%)	123 (27.5%)
Females (%)	376 (73%)	12 (86%)	8 (80%)	2 (40%)	6 (86%)	24 (75%)	324 (72.5%)
Side							
Left	266 (51.9%)	4 (28.6%)	7 (70%)	2 (40%)	1 (16.7%)	20 (62.5%)	232 (52%)
Right	202 (39.4%)	8 (57.1%)	3 (30%)	3 (60%)	4 (66.7%)	5 (15.6%)	179 (40.1%)
Bilateral	45 (8.8%)	2 (14.3%)	0	0	1 (16.7%)	7 (21.9%)	35 (7.8%)
Size, mm	28 [18 – 39]	33 [30 - 60]	50 [38-57]	22 [16 - 28]	85 [46-63]	29 [21-35]	27 [17-38]
BMI, kg/m^2	28.8 ± 6.16	28.8 ± 6	26.7 ± 2.6	25.9 ± 7.9	30 ± 8.4	31.3 ± 5.3	28.7 ± 6.2
SBP, mmHg	138 ± 23	148 ± 20	142 ± 29	150 ± 27	138 ± 23	152 ± 22	137 ± 22
DBP, mmHg	86 ± 13	89 ± 11	85 ± 13	91 ± 13	89 ± 11	94 ± 15	85 ± 13
Plasma glucose, mmol/L	5.3 [4.7-5.9]	5.1 [4.5-6.7]	7.1 [5.8-8.5]	6.5 [4.9-7.0]	5.2 [4.8-5.8]	5.6 [4.8-6.1]	5.2 [4.7-5.9]
Total cholesterol, mmol/L	5.5 ± 1.3	6.5 ± 1.5	6.4 ± 1.4	4.9 ± 1.0	5.7 ± 1.1	5.7 ± 1.0	5.5 ± 1.3
HDL cholesterol, mmol/L	1.34 ± 0.39	1.27 ± 0.48	1.77 ± 0.54	1.68 ± 0.40	0.97 ± 0.40	1.30 ± 0.34	1.33 ± 0.38
Triglycerides, mmol/L	1.34 [0.92- 1.96]	2.38 [1.08-2.75]	1.71 [1.04-2.36]	1.26 [0.96-1.48]	2.09 [1.58-2.91]	1.63 [0.99-2.21]	1.31 [0.90-1.91]
Uric acid, μmol/L	312 ± 101	339 ± 76	309 ± 63	368 ± 7	501 ± 101	312 ± 80	311 ± 104

during the evaluation of conditions that could be related to hypercortisolism - in two of them the adrenal tumour was detected because of lumbar pain and vertebral fractures, another two had been investigated for pneumonia and one patient presented with duodenal ulcer bleeding. Evident adrenal insufficiency was observed in 5 patients after adrenalectomy. Three of the seven patients with adrenal carcinoma also presented with hypercortisolism.

Besides lack of suppression after dexamethasone, the most common abnormality in patients with SCS was elevated urinary free cortisol - observed in 68% (22 out of 32 patients), followed by low ACTH in 64% (16 out of 25) and disturbed diurnal rhythm in 33% (10 out of 30). 14 patients (44%) had abnormal results in three or more tests of the HPA axis. Isolated abnormalities of HPA function were found also in patients who didn't meet the criteria for SCS and were considered as having NFAA. Suppressed ACTH was the most frequent abnormal test and was observed in 25% of patients (41 out of 161), non-suppressible cortisol after 1 mg DST was present in 20% (16 out of 81), elevated urinary cortisol excretion was found in 11% (41 out of 364) and the circadian cortisol rhythm was disrupted in 3% of patients with NFAA (6 out of 235). The combination of low ACTH and elevated UFC was detected in 6 patients and another 3 subjects presented with abnormal cortisol rhythm and excretion. All these patients achieved cortisol suppression below 50 nmol/L after 1 mg dexamethasone and thus did not qualify for SCS.

The prevalence of metabolic disorders and hypertension in patients with SCS and NFAA is depicted in Table 2. No statistically significant differences were observed for the rates of obesity, diabetes, IGT, metabolic syndrome and hypertension between the two groups although values were slightly higher in subjects with SCS. When compared with data from the general Bulgarian population the prevalence of hypertension, type 2 diabetes and metabolic syndrome was markedly increased in patients with NFAA (Table 3). The significant differences were evident in all age groups for hypertension, in the young and middle-aged subjects for type 2 diabetes and in the young patients for metabolic syndrome.

Table 3. Prevalence rates of arterial hypertension, type 2 diabetes and metabolic syndrome in patients with non-functioning adrenal adenomas (NFAA) and data from the general Bulgarian population [29,30].

	NFAA	General population	
Hypertension	78% (349/447)	43.8% (1051/2400)	p<0.0001
≤44 years	48% (48/100)	19.3% (206/1067)	p<0.0001
45 – 59 years	82% (161/197)	56.2% (478/850)	p<0.0001
≥ 60 years	93% (140/150)	76% (389/487)	p<0.0001
Diabetes mellitus type 2	17% (75/447)	8.37% (201/2400)	p<0.0001
≤44 years	8% (8/100)	1.87% (20/1071)	p=0.0016
45 – 59 years	17% (33/197)	9.0% (77/857)	p=0.0027
≥ 60 years	23% (34/150)	21.53% (104/487)	NS
Metabolic syndrome	36% (162/447)	30.8% (743/2409)	p=0.0024
≤44 years	26% (26/100)	13.7% (146/1069)	p=0.0018
45 – 59 years	40% (78/197)	38.8% (331/853)	NS
≥ 60 years	39% (58/150)	54.6% (266/487)	p=0.0007

Table 2. Prevalence rates of arterial hypertension and metabolic disorders in patients with non-functioning adrenal adenomas (NFAA) and subclinical Cushing's syndrome.

	NFAA (n=447)		SCS (n=32)		
	Males	Females	Males	Females	
Arterial hypertension	349 (78%)		28 (88%)		p=0.26
	92 (75%)	257 (79%)	6 (75%)	22 (92%)	
Obesity	149 (33%)		15 (47%)		p=0.13
	32 (26%)	117 (36%)	0	15 (63%)	
Metabolic syndrome	162 (36%)		13 (41%)		p=0.71
	41 (33%)	121 (37%)	2 (25%)	11 (46%)	
Diabetes mellitus type 2	75 (17%)		9 (28%)		p=0.14
	22 (18%)	53 (16%)	1 (13%)	8 (33%)	
Impaired glucose tolerance	24 (5%)		1 (3%)		p=1.00
	4 (3%)	20 (6%)	0	1 (4%)	
Dyslipidaemia	221 (49%)		19 (59%)		p=0.36
	56 (46%)	165 (51%)	5 (63%)	14 (58%)	

The adrenal tumour was larger than 40 mm in 89 patients with NFAA and 3 patients with SCS and this was the most common indication for surgery in these groups. Adrenalectomy was performed in 102 patients (96 with NFAA and 6 with SCS). The histological diagnosis revealed corticomyelolipoma in 4 patients and one tumour was found to be highly differentiated liposarcoma.

Follow-up data were available for 142 patients with NFAA and SCS and median follow-up duration was 18 months (range 3 - 144) (Table 4). 40 patients (38 with NFAA and 2 with SCS) were evaluated both at baseline and after adrenalectomy. In both patients with SCS the results from the tests of the HPA axis normalized after surgery but only one achieved also reduction in blood pressure. The remaining 102 patients who were not operated had benign adrenal adenomas smaller than 40 mm. Increase in tumour size of at least 5 mm was documented in 16 patients (16%) with NFAA while reduction of adenoma dimensions was observed in 3 subjects (3%). In two patients the control radiological evaluation failed to identify an adenoma. In the course of the follow-up two patients developed and adenoma in the contralateral adrenal gland. In 3 patients with NFAA the increase in tumour size was considered significant and they underwent adrenalectomy. Regarding the functional status none of the patients with NFAA developed overt hormonal hypersecretion of any kind and none of subjects with SCS advanced to overt Cushing's syndrome. During the follow-up three patients developed impaired glucose tolerance and another three were diagnosed with type 2 diabetes in the group with NFAA. New cardiovascular or metabolic disorders were not observed in patients with SCS. Two patients who were initially considered to have NFAA later developed SCS. On the other hand, another two patients whose results were consistent with SCS at baseline achieved cortisol suppression below 50 nmol/L after dexamethasone during subsequent investigations.

4. Discussion

Modern imaging modalities have made the encounter with adrenal tumours a common event in clinical practice. Approaches to the management of these adrenal incidentalomas (AI) are mainly governed by the need to identify potential malignant diseases and endocrine hyperactivity. Large unbiased studies on which management recommendations can be based are however relatively few [31-33]. In the current study we present the clinical and functional characteristics, some metabolic aspects and follow-up data of a series of 515 patients with AI evaluated at a single endocrinological centre using a unified management protocol.

The magnitude of the problem is easily illustrated by the 12-fold increase in the annual number of evaluated patients from the mid 1990s to 2010 reflecting the improved accessibility to high-resolution scanners in this time period as well as the increased awareness of physicians about AIs. The condition can be diagnosed throughout all age groups but the distribution curve is skewed towards the elderly with peak incidence in the sixth decade. This is not surprising since autopsy studies have demonstrated a positive relation of the prevalence of adrenal nodules and advancing age [2]. More-

Table 4. Characteristics of followed-up patients with non-functioning adrenal adenomas and subclinical Cushing's syndrome.

	Non-functioning adrenal adenomas (n=132)		Subclinical Cushing's syndrome (n=10)	
	At baseline	At last follow-up	At baseline	At last follow-up
Tumour size (mm)				
Operated	40 [28-53]	-	26 [20-31]	-
Non-operated	21 [15-30]	22 [15-30]	29 [19-35]	29 [17-34]
Plasma glucose, mmol/L				
Operated	5.1 [4.9-5.9]	5.0 [4.5-5.5]	6.3 [5.8-6.8]	5.0 [4.9-5.0]
Non-operated	5.0 [4.7-5.7]	5.3 [4.9-5.9]	5.1 [4.6-5.6]	5.4 [4.7-5.9]
Total cholesterol, mmol/L				
Operated	5.63 ± 1.38	5.74 ± 1.41	4.45 ± 0.62	5.13 ± 0.00
Non-operated	5.45 ± 1.15	5.51 ± 1.22	5.61 ± 0.96	5.90 ± 1.44
Triglycerides, mmol/L				
Operated	1.32 [0.87-1.94]	1.18 [0.93-1.76]	1.42 [0.60-2.24]	1.84[1.80-1.89]
Non-operated	1.36 [0.89-1.92]	1.34 [0.91-1.86]	1.38 [1.28-2.17]	1.30 [1.05-1.91]
Prevalence of hypertension				
Operated	24/38 (63%)	23/38 (61%)	1/2 (50%)	1/2 (50%)
Non-operated	83/94 (88%)	85/94 (90%)	7/8 (88%)	7/8 (88%)
Prevalence of diabetes				
Operated	4/38 (11%)	5/38 (13%)	0/2 (0%)	0/2 (0%)
Non-operated	16/94 (17%)	18/94 (19%)	1/8 (13%)	1/8 (13%)
Prevalence of metabolic syndrome				
Operated	12/38 (32%)	11/38 (29%)	2/2 (100%)	2/2 (100%)
Non-operated	38/94 (40%)	44/94 (47%)	3/8 (38%)	3/8 (38%)

over, diagnostic imaging is more frequently performed in the elderly patients. Although autopsy data show no sex differences we observed a strong female predominance (73% vs 27%) which is in accordance with other published series [1,4,31] and is most likely due to referral bias as women more often undergo radiological investigations because of higher prevalence of biliary disease and gynecologic disorders. Contrary to other reports [1,31,34], however, in our cohort the left adrenal gland was more frequently affected. The higher proportion of right-sided lesions in some studies is usually explained by the prevailing use of ultrasound as initial examination as this technique is less effective for visualization of tumours especially smaller ones in the left adrenal gland [35]. The greater part of AIs in our series was detected by CT or MRI providing a possible answer to the observed phenomenon.

The hormonal evaluation of incidentally found adrenal tumours revealed that the large majority (82.9%) are benign non-functioning adrenal adenomas and the prevalence of overt endocrine hyperfunction is relatively low (5.6%). Earlier studies have reported higher proportion of hypersecreting tumours but some of them suffer from different forms of bias such as including patients from surgical and oncology series, excluding patients with small tumours or patients with non-functioning tumours, or analyzing small number of patients. A recent prospective study in Sweden including unselected patients from radiological departments estimated the prevalence of hormonally active tumours at 3.1% [32]. A meta-analysis deliberately excluding studies with potential selection bias also confirmed the previous overestimation of the prevalence of hypersecreting lesions by showing that they represent less than 10% of AIs [36]. Furthermore, it has been shown that the frequencies of pheochromocytoma, cortisol- and aldosterone-producing tumours have not undergone significant changes since the introduction of computer tomography [37] and the increased detection of adrenal incidentalomas is mainly due to the identification of benign non-functioning adenomas therefore leading to a fall in the relative proportion of functioning masses. Nevertheless the recognition of these conditions is of vital clinical importance since patients can benefit from early and possibly definitive cure. It should be noted that in our study almost all patients with overtly hypersecreting lesions (except two patients with pheochromocytoma) exhibited some of the clinical features typical for the respective disease and it can be argued whether these tumours can be truly termed “incidentalomas”. Our decision to include them in the analysis was based on the fact that their condition was not suspected until the detection of the adrenal mass. This also means that some mild and oligosymptomatic forms of hypercortisolism, hyperaldosteronism and catecholamine excess remain underdiagnosed with all subsequent unfavorable effects for the patients.

In agreement with the other contemporary reports [32,36] we found a low prevalence (1.6%) of primary adrenal carcinoma among patients with AI. The observed percentage may however underestimate the true frequency of the condition as some large tumours with invasion of adjacent tissues or distant metastases at the initial radiological examination may have been directly referred to surgical departments thus escaping prior endocrinological evaluation.

The issue of subclinical autonomous glucocorticoid secretion remains one of the most controversial and debated topics in the evaluation of AI. The difficulties in defining the condition of SCS stem from the lack of clear differentiation of what is “clinical” and “subclinical”cortisol excess and therefore diagnosis is based only on laboratory tests none of which are 100% sensitive and specific. Cortisol secretion in adrenal adenomas follows a gradual continuum from normal to autonomous [38] and the prevalence of SCS obviously depends on where the threshold of normality has been set. The clinical manifestation is additionally blurred by variations in the sensitivity to glucocorticoids [39]. In order to provide a diagnostic standard, the NIH position statement in 2002 recommended the use of 1 mg dexamethasone suppression test as a means of identifying autonomous cortisol production [8]. Cortisol cutoff values ranging from 27.5 to 138 nmol/L have been used by different investigators further widening the spectrum of the reported prevalence of the disorder [40]. The suggested by NIH threshold of 138 nmol/L yields good specificity but may miss some patients because of low sensitivity. In the present study we chose to use cortisol cutoff level of 50 nmol/L recommended for screening of overt Cushing’s syndrome [41] and eliminated the potential false-positive results by employing a second test of the HPA axis. By using these criteria we identified 32 patients (5.94%) with SCS, making this condition the most common hormonal disturbance in subjects with AI. An interesting observation is also the increased prevalence of SCS in bilateral adrenal adenomas.

Chronic exposure even to mild glucocorticoid excess is supposed to predispose to some of the classic consequences of long-term hypercortisolism and indeed increased prevalence of hypertension, diabetes, insulin resistance, higher risk of osteoporosis and vertebral fractures have been observed in patients with SCS [12,13,42]. In the present study, however, we did not find any significant differences in the occurrence of metabolic disorders and hypertension between patients with SCS and non-functioning adenomas and

similar results have been also described in other recent studies [43,44]. The association of subclinical cortisol autonomy and the development of metabolic derangements is further shaken by the conflicting results that come from series in which adrenalectomy has been undertaken. Some authors describe improvements in metabolic parameters after surgery [45,46], while others do not find any amelioration of cardiovascular risk factors [16,43,47]. These discrepancies are probably due to different definitions and criteria for SCS or small sample sizes. A limitation of our study is the small number of patients with SCS who were followed-up after adrenalectomy which prevents us from making a firm conclusion about the effect of surgical treatment.

Despite being usually related to cortisol excess in SCS, in our study hypertension, type 2 diabetes and metabolic syndrome were much more common also in patients with non-functioning adrenal adenomas compared to the general Bulgarian population. A clear explanation of these observations cannot be provided by our current knowledge. Potential selection bias cannot be entirely excluded since these conditions are very frequent in the elderly population and it may be speculated that patients suffering from such disorders are more likely to be subjected to abdominal imaging. The increased prevalence of hypertension and metabolic derangements was however observed throughout all age groups and was especially well marked in younger patients. Intermittent hypercortisolism or secretion of precursor molecules may be responsible for at least a part of the cases and such presumption is supported by the frequent detection of isolated suppression of ACTH. On the other hand, in a recent study we demonstrated that the levels of steroid precursors of the glucocorticoid pathway were not altered in a series of 88 consecutive patients with AI [48]. An alternative hypothesis is that adrenal adenomas may be a consequence of an insulin resistance state that also predisposes to arterial hypertension and diabetes since hyperinsulinemia has been identified as a mitogenic factor for adrenal cortical cells [49]. Moreover, age and hypertension related atherosclerotic changes in supplying arterial vessels may lead to cortical atrophy followed by compensatory nodular hyperplasia especially in elderly patients. Until the elucidation of this issue it may be suggested that patients with AI even without overt or subclinical hormonal secretion should be evaluated for the presence of hypertension and metabolic disorders and managed according the available recommendations for the respective conditions.

During the course of follow-up patients with NFAA featured stable tumour size and tumour growth was documented in a small number of patients (16%) and in even fewer patients (3%) it was significant for an indication for surgery. The hormonal status also did not show considerable fluctuations and progression to overt hypersecretion was observed neither in patients with NFAA nor in subjects with SCS.

In conclusion, the results of our study indicate that adrenal incidentalomas are increasingly detected in recent years with benign non-functioning adrenal adenomas being the most common. The prevalence of primary adrenal malignancy and overtly hypersecreting tumours such as pheochromocytoma, cortisol- or aldosetrone-producing adenomas is relatively low but their identification at initial evaluation is mandatory so that patients can be appropriately treated. Although being the most common abnormality in patients with AI, the clinical significance of SCS remains questionable as neither its definition nor its management are clearly determined. Until stronger evidence is available treatment decisions should be based on individual judgment taking in consideration patients' age, severety of HPA abnormalities and presence of hypercortisolism-related complications. Adequately-designed prospective studies are needed for the clarification of the underlying pathophysiological mechanisms behind the observed association of non-functioning adrenal adenomas and metabolic disturbances and the evaluation of the potential cardiovascular risks.

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