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Original Research

The Hormonal Status Comparison of Unilateral and Bilateral Adrenal Adenomas: Are They the Same?

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ABSTRACT

Objective: It is not yet clear whether unilateral/bilateral adenomas are different in terms of both functionality and etiology. We investigated whether there were differences in hormonal profiles and evaluate the cortisol secretion profiles of unilateral and bilateral adenomas.

Material&Methods: Hormonal secretory profiles and clinical features of patients with adenomas were collected. Detailed evaluation was made in terms of hypercortisolemia.

Results: Of the 184 patients examined, 140 had unilateral and 44 had bilateral adenomas. 73% of the patients were female and the mean body mass index was 34±8.1kg/m^2. The mean age was 57.1±9.8 years. The average size of the adrenal masses was 23.3±10.5mm. While 83% of the evaluated adenomas were nonfunctional, ACS was found in 11% (n:20), hyperaldosteronism in 4% (n:8), and pheochromocytoma (PCC) in 2% (n:3) of the patients. The prevalence of ACS in bilateral/unilateral adenomas was 20.5%/7.9%, respectively. While serum adrenocorticotropic hormone level (25.6±16.6vs19.3±15µg/dL), urinary free cortisol level (162.3±108.3vs243.3±234.2µg/day), and low-dose-dexamethasone-suppression-test results (1.6±1.9vs1.73±1.7µg/dL) were not statistically different, the only difference between unilateral and bilateral adenomas was in serum DHEA-S level (141.4±85vs77.7±73.8 µg/dL, p:0.003).

Conclusion: Although there is no significant difference between the two groups in terms of clinical findings, it is clear that ACS is more prevalent in bilateral adenomas than unilateral. Because of the negative effects of long-term hypercortisolism, precise management of ACS is noteworthy. The evaluation of ACS should be done more carefully in bilateral adenomas considering that ACS is more in bilateral adenomas than unilateral. According to our findings, we also suggest that DHEA-S may be an indicator for ACS.

Keywords: autonomous cortisol secretion, bilateral adrenal adenomas, Dehydroepiandrosterone Sulfate

INTRODUCTION

Adrenal incidentalomas are tumors of the adrenal gland, mostly found incidentally in imaging modalities of unrelated purposes and greater than 1 cm. The more frequent use of imaging methods such as magnetic resonance imaging (MRI) and computerized tomography (CT) has led to an increased incidence of adrenal incidentalomas [1]. The incidence of adrenal incidentalomas is about 3 % in the middle-aged patient population, whereas it

reaches up to 10% in elderly patients [2].

Adrenal incidentalomas, mostly unilateral, can be bilateral in 10-21% of various studies [3-5]. Although there is much known about unilateral adenomas, there is less information about bilateral adenomas. Interestingly, bilateral adenomas are more common than having two or more adenomas in the same adrenal gland [6]. In a few published articles, bilateral incidentalomas of adrenal glands were different from unilateral in terms of both functionality and etiology [3,7]. It has also shown that if the mechanism had been the same, the prevalence of adenomas in both adrenal glands would be much lower than in the current situation [6]. The most common causes of bilateral adrenal masses are metastases, primary bilateral macronodular hyperplasia, and adenomas [8].

When these frequently encountered lesions are observed in imaging techniques, there are two primary questions to be answered. These questions are 1) Does it have malignant potential and 2) Does it have no hormonal function? [8].

Malignant masses in the adrenal gland may be either primary carcinoma of the adrenal gland or metastases of various cancers. Although primary adrenocortical carcinoma (ACC) is extremely rare (0.72 cases per million), up to 10% of these cases are bilateral. The point of attention in metastases in the adrenal gland is the risk of bilaterality and the potential for adrenal insufficiency [9]. When adrenal incidentalomas are evaluated in terms of functionality, while only a small proportion have apparent hormone secretion and associated clinical stigmas, the vast majority are nonfunctioning and asymptomatic. However, several studies in the last decades have shown that some of these non-functional and asymptomatic tumors have hormone secretion, particularly cortisol [10,11]. Excessive cortisol release without evidence of clinical symptoms was called subclinical Cushing's syndrome or subclinical hypercortisolemia in previous years and was first described by Charbonnel et al. [11]. However, it was thought that these nomenclatures did not reflect the disease condition, and it was named autonomic cortisol secretion (ACS) in 2016 [12]. It was shown that the risk of fragility fractures, arterial hypertension, diabetes mellitus (DM), and metabolic syndrome is increased in ACS [13,14]. In addition to that, improved DM, hypertension, lipid metabolism, and obesity were observed in affected patients after unilateral adrenalectomy but not for osteoporosis in a prospective study [15]. In a meta-analysis published in 2016 comparing surgery and conservative treatment, the patients in the surgical arm had higher recovery rates in DM and hypertension, while there were no significant differences in the improvement of dyslipidemia and obesity [16]. Moreover, another critical aspect is that ACS is much more common than adrenal Cushing's syndrome with a wide range of frequency (5-30%) depending on the criteria used for ACS diagnosis in various studies [17].

There is a current trend for bilateral and unilateral incidentalomas to be evaluated as different entities in terms of origin and functionality in recent years. Therefore, we retrospectively evaluated our cases to compare these unilateral and bilateral adrenal masses regarding hormonal and malignant potentials. We also evaluated the frequency of ACS in our cohort.

Main Points;

- Adrenal adenomas are detected bilaterally between 10-20% and they are thought to differ from unilateral adenomas in terms of hormonal functionality.
- In our study, cortisol hypersecretion was found to be more common in bilateral adenomas.
- The risk of cortisol hypersecretion is higher, especially in patients with low dehydroepiandrosterone sulfate (DHEA-SO4) measured at baseline tests.
- Treatment approach in patients with bilateral adenoma and cortisol hypersecretion is still unclear and prospective studies are still needed on this subject.

MATERIALS AND METHODS

Patients

In this study, 204 patients admitted to tertiary endocrinology clinics between 2005 and 2014 with the diagnosis of adrenal incidentaloma were evaluated. Presence of overt Cushing syndrome or Cushing's disease, diseases (alcoholism, major depressive disorder, renal and hepatic failure) or drugs that affect the dexamethasone suppression test (DST) and steroid metabolism, and patients with a history of chronic steroid intake, oral contraceptives, and postmenopausal hormonal replacement treatment were excluded (Figure 1). Twenty patients were excluded according to radiological findings such as non-adenoma adrenal pathologies. Patients with a history of malignancy were also excluded. The remaining 184 patients were divided into two groups: unilateral and bilateral adenomas. The study was approved by the local Ethical Committee of Ankara University Faculty of Medicine (04-179-15/9/3/2015).

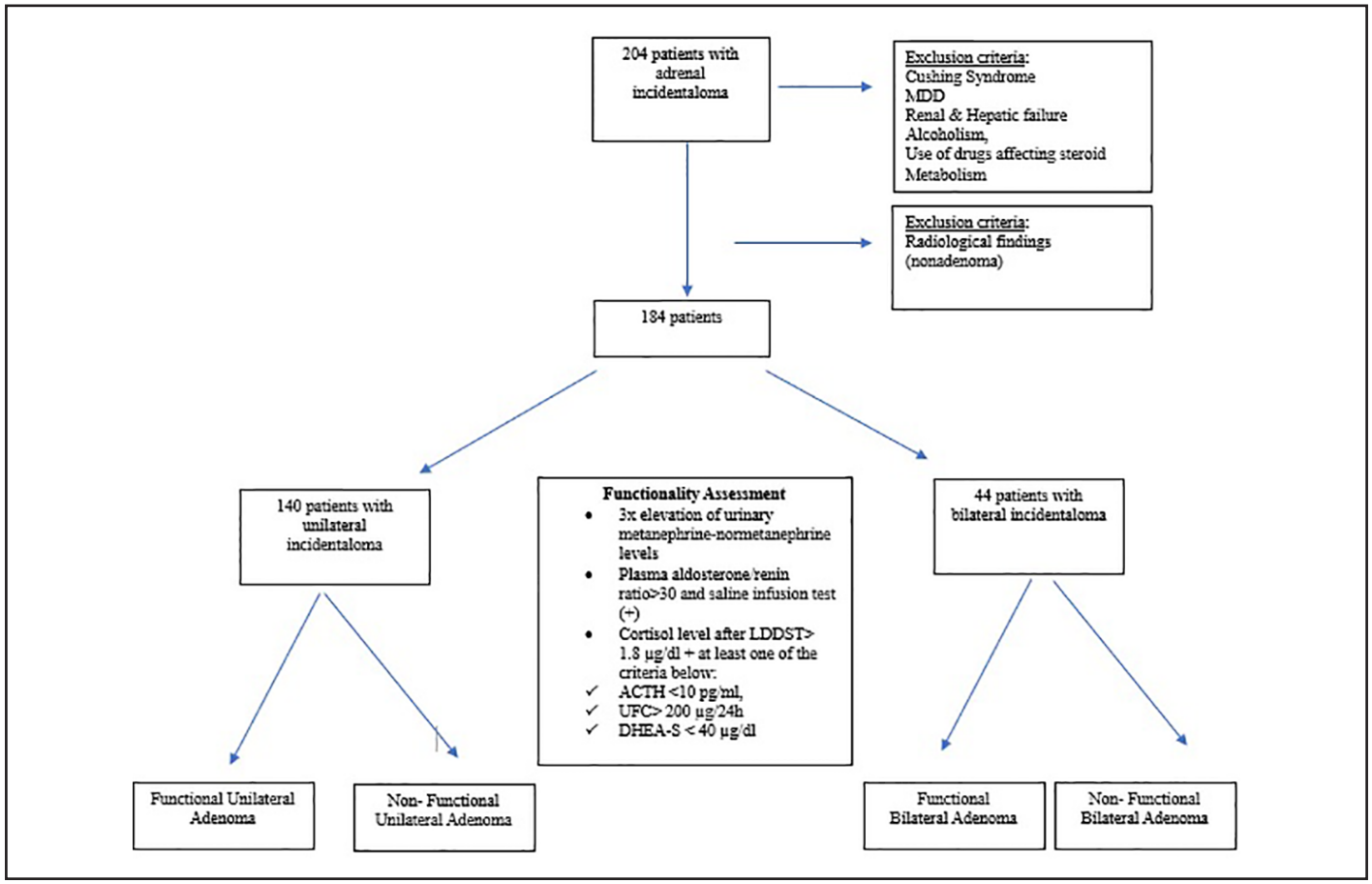

Figure 1. Flow chart of patients included in the study
Abbreviations: **MDD:** Major Depressive Disorder, **LDDST:** Low Dose Dexamethasone Suppression Test, **ACTH:** Adrenocorticotropic hormone **UFC**: Urinary Free cortisol, **DHEA-S** Dehydroepiandrosterone-Sulfate

Hormonal and Biochemical Assessment

Blood samples were obtained from each patient in the morning after 12 h of fasting to measure routine complete blood count (CBC) analysis and biochemistry panel.

Serum adrenocorticotropic hormone (ACTH), cortisol, dehydroepiandrosterone sulfate (DHEA-S), total testosterone, aldosterone levels, plasma renin activity, urine metanephrine, and normetanephrine levels, and urinary free cortisol levels were also measured to assess the hormonal activity.

Serum cortisol concentrations were ascertained by immunoenzymatic assay (Beckman Coulter, Access Immunoassay Systems, Access cortisol assays, USA). The intra-assay coefficients of variation (CV) were less than 5%. We ascertained urinary free cortisol by radioimmunoassay (DIAsource Immunoassays S.A., Belgium), and the intra-assay CV was less than 7%. The serum ACTH concentration was measured by electrochemiluminescence immunoassay (Roche Elecsys 2010 analyzer, Roche Elecsys-ACTH), and the intra-assay CV was less than 6%. DHEA-S was measured using diagnostic kits obtained from Beckman Coulter by chemiluminescent immunoassay (Beckman Coulter, Access Immunoassay Systems, USA), and the intra-assay CV was less than 8.3%.

Free cortisol measurement in 24-hour urine and DSTs were conducted in patients suspected to have Cushing's syndrome and ACS via 1 and 2 mg.

At least one of the following criteria was adopted to diagnose ACS as the cortisol value was above 1.8 µg/dl after 1 mg DST: ACTH <10 pg/ml, urinary free cortisol (UFC) > 200 µg/24h, DHEA-S < 40 µg/dl [5].

Statistical Analysis

Data were statistically analyzed using SPSS (SPSS for Windows, Version 15.0. Chicago, SPSS Inc.) statistical software. The data were expressed as mean ± SD. The distribution of parameters among groups was investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test). Categorical parameters were evaluated using the chi-square test. Since the distribution of these subdivisions was normal according to the visual and analytical methods, two groups were compared using independent T-tests, and one-way analysis of variance (ANOVA) tests were performed comparing four groups for continuous variables. An overall p-value of less than 0,05 was considered to show a statistically significant result. When overall significance was observed, the pairwise post hoc test was performed using the Bonferroni test. A logistic regression model was created and used for multivariate analysis to evaluate the risk factors for ACS development. In the model created, bilateral adrenal adenoma development was evaluated in groups with autonomous cortisol secretion according to age and BMI.

RESULTS

Patient characteristics

184 patients were included in the analysis. Written informed consent was obtained from all patients. The male-to-female ratio was M/F: 27/73% (48 male and 136 female), the mean age was 57.1 ± 9.8, and the mean body mass index (BMI) was 34 ± 8.1. In 88 % of the patients, the diagnosis and follow-up of the adrenal adenoma were performed by CT, while the method used in 12 % of the patients was MRI. The average size of the adrenal masses was 23.3±10.5 mm. While 83 % of the evaluated adenomas were nonfunctional, ACS was found in 11% (n:20), hyperaldosteronism in 4% (n:8), and pheochromocytoma (PCC) in 2% (n:3) of the group. The patients were evaluated with either CT or MRI twice a year for follow-up of tumor growth. No increment in tumor sizes was noted during follow-up. The two patients were operated on because the tumor size (with a great dimension of 55 mm) did not reveal malignant histopathology. PCC was detected in a patient who was operated on for a 60-mm unilateral adenoma.

Evaluation of unilateral and bilateral adenomas

No significant difference was found between the two groups in terms of age, gender, BMI, and mass size, as shown in Table 1. There was no significant difference between the two groups for the low-dose dexamethasone suppression test (LDDST), UFC, and ACTH. On the other hand, DHEA-S was found to be lower in bilateral adenomas than in unilateral adenomas (77.7 ± 73.8 vs. 141.4 ± 85, p: 0.003).

Functional evaluation of 140 patients with unilateral adrenal incidentaloma revealed ACS in 11 patients, Conn's syndrome in 6 patients, and PCC in 2 patients. Of the 44 patients with bilateral adrenal adenoma, 9 had ACS, 2 had Conn's syndrome, and one had PCC. In our evaluation of 184 included patients, ACS was present in 7.9 % (11/140) and 20.5 % (9/44) in unilateral and bilateral adrenal adenoma patient groups, respectively. This result was statistically significant (p= 0.027), and the odds ratio was calculated to be 3.01 (CI 1.1-7.8) for comparing the two groups. As shown in Table 2, this ratio was 3.07 when age and BMI-adjusted values were used. However, when we investigated whether this situation had a clinical reflection in patients, no significant difference was found between the two groups in terms of metabolic disorders due to cortisol excess such as hypertension, IFG, DM, and dyslipidemia.

The evaluation of patients with and without ACS

Considering the clinical features of the patients (Table 3), there was no difference between patients with ACS and patients with non-functional adrenal adenomas in terms of hypertension (55% vs. 31%, p:0.06) and dyslipidemia (73.7% vs. 70.1%, p:0.74) frequency. However, it was observed that IFG/DM was more common in patients with ACS (45% vs. 17.4% p:0.01). Although the mean greatest dimensions of adenomas with ACS were larger than non-functional adenomas, there was no statistically significant difference (26.4±11 vs. 22.5±10.1, respectively p:0.11). In addition to post-LDDST nonsuppressed cortisol (4.54 ± 3.5 vs 1.16 ± 0.5; p< 0.001) in patients with ACS, a significant decrease in DHEA-S (61.4 ± 38.5 vs 106.6 ± 79 p= 0.02) was observed.

Evaluation of bilateral and unilateral adenomas according to the presence of ACS:

Considering the clinical characteristics of the patients; there was no significant difference in age, gender, mass size, BMI, dyslipidemia, DM, and hypertension in the subgroup analysis of patients who were divided into four groups according to the presence of bilaterality and ACS (unilateral ACS -, unilateral ACS +, bilateral ACS -, bilateral ACS +) (Table 4). Besides these, in the examination of patients' laboratory characteristics, the cortisol values after LDDST (1.17 ± 0.5; 5.73 ± 3.9; 1.1 ± 0.4; 3.1 ± 2.7 respectively, p<0,001) and DHEA-S (141.7 ± 87; 62.1 ± 35.3; 69.4 ± 46; 40.8 ± 43.2 respectively, p:0.01) measurements were found to be different. In the binary analysis, as expected,

the cortisol value after LDDST was found to be significantly higher in the ACS (+) than in the ACS (-) two groups. In addition, DHEA-S levels were lower in bilateral adenomas than in unilateral ACS (-) adenomas (Table 4).

Logistic Regression Analysis: In age- and BMI-adjusted logistic regression analysis, bilaterality was correlated with ACS (p=0,039).

DISCUSSION

The frequency of adrenal incidentalomas has increased since it was first described in 1941. Although they were initially thought to be hormonally nonfunctioning, up to 20% of adrenal incidentalomas secrete hormones [15]. ACS is reported in adrenal incidentalomas with a 5–30% prevalence, depending on the screening procedures in numerous studies [17]. Numerous studies have shown that even if ACS does not lead to prominent clinical findings, it may cause comorbidities of cortisol release. Thus, this clinical condition necessitates the diagnosis and strict follow-up of this entity.

One of our major findings was the higher frequency of ACS in patients with bilateral adrenal adenoma than unilateral adrenal adenoma (20,5% vs. 7,9 %, respectively, p: 0.027). Paschou and colleagues reported that ACS prevalence was increased in bilateral adrenal incidentalomas vs. unilateral adenomas in a recent meta-analysis. They argued on the difference in cortisol chronobiology regulation between unilateral adrenal incidentalomas and bilaterals [18]. Current genetic trials conducted within the past few years have found that etiologies of bilateral adrenal adenomas might be different from one another [6,19]. Bilateral and unilateral adenomas also have different molecular backgrounds and may impact cortisol-related comorbidities [20].

The increasing prevalence of ACS in bilateral adrenal tumors poses a challenge for clinicians to diagnose [20]. Although there is no radiological guidance for bilateral incidentalomas, hormonal evaluation becomes more critical in their evaluation and follow-up. Moreover, ACS diagnosis relies on clinical evaluation, and the nature of the disease is asymptomatic; specific parameters to assess this entity are an obligation. Until now, some clinical biomarkers and tests have been utilized to differentiate between cortisol- and non-secreting adenomas, especially in patients with bilateral adrenal incidentalomas. Early morning ACTH, urinary-free cortisol, midnight salivary cortisol, and LDDSTs are the most common tests studied for ACS. Because of its short half-life and pulsatile secretion, ACTH has low sensitivity and specificity in detecting ACS [21]. Although plasma ACTH levels are generally low in ACS, there is an overlap with ACTH levels in healthy individuals [22]. Also, 24-hour urinary free cortisol (UFC) has poor specificity and false positivity in detecting ACS [23]. In our study, we could not find a difference in ACTH, urinary free cortisol, and LDDST between unilateral and bilateral adrenal adenomas, and only LDDST and DHEAS were different among the non-functional and ACS groups.

Other potential markers were proposed for a possible ACS marker in patients with AI because of all the above-mentioned circumstances. DHEAS was one of the most implemented markers for the diagnosis of ACS. The proposed mechanism of the usage of this marker is the reductive effect of the central suppression of ACTH on DHEAS [24]. It is a more reliable test because of its prolonged half-life and stable level during day [23]. Previous studies suggested suppressed levels of DHEAS as a potential indicator of ACS [5,25]. Yener et al. reported an age-unadjusted DHEAS threshold of 40.0 mcg/dL with a sensitivity of 68% and a specificity of 75% for the diagnosis of ACS [5]. We found a significant difference between unilateral adenomas vs. bilateral adenomas and nonfunctional adenomas vs. ACS. Bilateral ACS had the lowest levels of DHEAS with a mean level of 60.8 ± 43.2 μg/dL (p:0.01). This finding supports the use of DHEAS as a diagnostic criterion for ACS, especially for bilateral adrenal incidentalomas. Despite nonsuppressed cortisol values after 1 mg DST being the most accurate test to diagnose ACS, we required the presence of at least one additional hormone abnormality (ACTH suppression, low DHEA-S, high UFC).

Another significant finding of our study was that there was no difference in mass size among groups of patients with and without ACS. The mass sizes were larger than nonfunctional adrenal masses, but they did not reach statistical significance. Most previous studies reported larger adrenal masses in patients with ACS [26-28]. They all suggested a relationship between cortisol secretion and mass volume in ACS. As the tumor diameter increases, the risk of autonomic cortisol-release increases in adrenal adenomas [26]. In contrast to these reports, we did not find such an association between mass size and hypercortisolism, which was compatible with a few previous studies [29,30].

Although the ACS rate in patients with bilateral adenoma

is higher than that in patients with unilateral adenoma, this does not appear to be clinically relevant. No statistically significant difference was found between the two groups in terms of diseases such as hypertension, DM/Impaired Fasting Glucose (IFG), and dyslipidemia, which we expect to occur due to hypercortisolemia. When the effects of ACS on clinical features were investigated, there was no difference in HT and dyslipidemia between patients with or without ACS, whereas DM/IFG was significantly higher in the ACS group. The most common clinical features of ACS are HT and impairment of glucose metabolism. There is an association between ACS and these metabolic derangements resulting from the direct and indirect effects of cortisol on the vascular system [21]. We could not find such an association for HT. There were also few studies reporting no relationship between ACS and HT [31,32]. The attributed mechanism for this finding was thought to be associated with a higher cut-off value of LDDST, but this could not be implemented in our findings because of our lower cut-off value for LDDST. We can only hypothesize that there might be cyclic secretion of cortisol in our ACS group, although we could not obtain such a finding. Also, the duration and degree of patients' exposure to high-dose cortisol may be a possible factor. Unfortunately, we do not have the long-term results of these patients because of the retrospective design of the study. Clinical manifestations are likely to occur in the long term in patients with autonomous cortisol secretion who remain untrained and untreated.

Although the primary pigmented nodular adrenocortical disease may rarely be seen as adenoma [33], our cases were evaluated by two different experienced radiologists and determined as adenomas. In these cases, biopsy or surgery may be the only way to make a definitive differential diagnosis. As we already know, adrenal biopsy is not generally the preferred method for diagnosing benign diseases of the adrenal gland, and even in biopsies performed to confirm the diagnosis of malignancy, high diagnostic success was not achieved.

One of the difficulties in the management of bilateral adrenal adenomas is the optimal treatment approach. In our patient group, only one patient undergoing bilateral adenoma underwent surgery. Today, surgery is still the only curative treatment for Cushing and ACS. However, postoperative morbidities of bilateral adrenalectomy are reported to be high (18%) in a previous paper [34]. In this case, an alternative to bilateral adrenalectomy was the follow-up of these patients without treatment. However, surgery benefits have been shown in patients with ACS in a prospective study [15]. The third option in these patients is to determine the side with dominant cortisol release and perform unilateral adrenalectomy. Similar to the adrenal venous sampling performed in primary hyperaldosteronism, it can be determined which adrenal glands dominantly secrete cortisol by measuring cortisol from both adrenal veins. In an article published by Young et al. evaluating ten patients with bilateral adenoma, it was seen that cortisol was secreted from one side in 5 of 10 patients [27]. No recurrence was detected during follow-up after unilateral adrenalectomy. However, this method is not standardized yet and more extensive prospective studies are needed.

No primary adrenocortical carcinoma was found in the patient group we examined. This may be because primary ACC cases, whose mass size reaches huge diameters at the time of diagnosis, are primarily evaluated in surgical clinics, and patients with a pre-diagnosis of adrenal gland metastasis are primarily evaluated in oncology clinics where they are followed up with a diagnosis of cancer. This data was consistent with previous studies, and studies in endocrine clinics showed that primary ACC and adrenal metastasis rates were low, and these rates may differ from those in surgical clinics [4,8]. In Dunnick's study, in which radiological features of adrenal masses were examined, it was seen that 10% of primary ACCs were bilateral [35]. There was no statistically significant difference in malignancy in the two patient groups we compared ($p>0,005$). However, it is not easy to say whether or not bilaterality is a risk factor for primary ACCs as it has an extremely low (0.72 per million) incidence [36]. Moreover, a study in which bilateral masses were followed for 12 years failed to show any evidence of an increase in the risk of long-term malignancy in bilateral masses [37].

There was a female predominance (136/48) in the patients included in our study. This predominance has also been observed in other retrospective studies of adrenal incidentalomas but not in autopsy studies [2,5,38]. Although there is a review showing that this gender difference is not only in adenomas but in all adrenal tumors, the factors causing this difference have not been fully elucidated, and it was thought that the reason why adenoma is more common in women may be due to the more frequent use of abdominal imaging in women [38].

The limitations of our study were the retrospective design of the study and the lack of other supportive measures such as midnight

cortisol or salivary cortisol measurements. We did not evaluate patients for cardiovascular status or bone metabolism because of the possible deleterious effects of cortisol on the cardiovascular system and bone metabolism. Another limitation was the absence of a surgical evaluation of ACS patients. However, there were no clear surgical indications for our ACS patient group.

In conclusion, the presence of bilaterality is essential in the evaluation of adrenal adenomas. Although there was no significant difference in the size of the adenomas in the current study, functional evaluation became more critical in adenomas with both bilaterality and a size of more than 2 cm. Another important point in ACS patients is that the metabolic derangement may not always present in these patients. Therefore, the decision for the presence/absence of ACS should never be made solely based on clinical findings, and hormonal examination should be performed. DHEA-S, which has a low plasma level due to autonomous cortisol release, should be examined in the functional examination of patients with adrenal adenomas. Finally, why autonomous cortisol secretion is more common in bilateral adenomas is still unknown. Also, the treatment approach in these patients could not be clarified. Hence, more prospective studies are needed in this field.

Conflict of Interest: Authors have no conflict of interest to declare.

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Ethical Statement: The study was approved by the Clinical Research Ethical Committee of Ankara University Faculty of Medicine (04-179-15/9/3/2015).

Author Contributions: BO, AGC, and MS contributed to the study design. BO and CO contributed to the acquisition of data. BO, AGC, CO, and MS contributed to data analysis and interpretation. BO and AGC contributed to the drafting of the manuscript. BO, AGC, DC, and MS contributed to revise the manuscript. All authors have read and approved the final version of the manuscript.

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