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Evaluation of adenoma size and cortisol secretion status in patients with adrenal incidentalomas at long-term follow-up

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ABSTRACT

Context Increased prevalence of adrenal incidentalomas (AIN) necessitates clarification of optimal follow-up for benign adrenal adenomas without overt hormone excess.

Aim: To evaluate the radiological and hormonal assessment of AIN patients to determine the risk of malignant transformation, development of overt hormone excess or mild autonomous cortisol secretion (MACS) during long-term follow-up.

Materials and Methods: Retrospective cohort study. In a total number of 908 AIN patients, eligible 467 patients with adrenal adenomas were enrolled.

Results: Median age was 55 (21-85) years with a female dominance (73.4%). Median adenoma size was 20 (10-65) mm. Median follow-up duration was 60 (12-204) months. Increase in adenoma size was observed in 36.8% and significant increase (≥10mm) was observed in 4.7% of the patients. Development of overt hormone secretion or adrenocortical carcinoma was not detected while 13 patients with NFA (3.9% of NFA) transformed to MACS and 3 patients with MACS (10.2% of MACS) transformed to NFA at follow-up. Among 13 patients transformed from NFA to MACS, 39% featured ≥10mm increase in adenoma size while this was 4% in patients with stable cortisol secretion level during follow-up ($p<.001$). Transforming from NFA to MACS at follow-up was the strongest independent predictor of an increase ≥10mm in size in multivariate analysis [Beta: 2.352, OR(CI%): 10.5- (2.8-39.2), $p< .001$].

Conclusion: Incidentally discovered adrenal adenomas feature a stable course in terms of adenoma size and hormonal status. However, given our findings demonstrating an interrelation between adenoma enlargement and MACS development, follow-up radiological and hormonal work-up should be individualized.

Introduction

Adrenal incidentalomas (AIN) are discovered serendipitously on imaging studies for unrelated conditions [1]. Their prevalence has been increasing related with the widespread use and advanced technology of cross-sectional imaging. In computed tomography (CT) scan series prevalence ranges from 1% to 5% and increases to 10% in older adults between 50 – 60 years of age [2,3]. The vast majority of AIN are benign and non-functioning adenomas. Mild autonomous cortisol secretion (MACS) is the most frequent hormonal alteration among individuals with AIN and occurs in approximately 10% of patients [4]. Individuals without clinical signs of Cushing's syndrome but fail to suppress serum cortisol below 50nmol/l on 1-mg overnight dexamethasone suppression test (DST) have been regarded as MACS. The clinical importance of MACS is related with the increased prevalence of unfavourable metabolic and cardiovascular conditions [5].

Surgical treatment of an AIN is mandatory when it is potentially malignant or functionally active. Functional activity includes pheochromocytomas, androgen secreting tumours, primary hyperaldosteronism (PHA) or overt Cushing's syndrome. Surgery in MACS is confined to patients with proven corticotrophin (ACTH) independency of cortisol autonomy and accumulated cortisol related co-morbidities which are difficult to treat, resistant to conventional treatment options, multiple, unusual or progressive [4]. Therefore, a significant number of AIN patients are not candidates for surgical treatment and offered clinical, hormonal and radiological follow-up.

The frequency and intervals of follow-up for an AIN mainly depends on the initial radiological appearance. Large masses particularly ≥ 4-6 cm or with low fat content necessitates frequent monitoring. Current guidelines do not recommend more than two cross-sectional imaging in lipid rich AIs which are smaller than 4 cm [4].

The increased prevalence of AIN necessitates clarification of optimal follow-up in patients with benign adrenal adenomas without overt hormone excess. For this purpose, in this study, we sought to evaluate the radiological and hormonal assessment of AIN patients to determine the risk of malignant transformation, development of overt hormone excess or MACS during long-term follow-up.

Materials and Methods

This retrospective cohort study was approved by the Ethics Committee of Dokuz Eylul University, Izmir, Turkey (2024/07/01). Data of all patients recorded between 2000 and 2024 in AI database of Dokuz Eylul University Endocrinology Division was evaluated.

Adrenal Incidentaloma Work-up

All patients referred underwent a diagnostic protocol including investigation of medical history, physical examination, endocrine work-up, routine laboratory investigations and cross-sectional imaging at baseline and each follow-up visit. The frequency of the follow-up visits was individualized.

Although several updates have been made for the approach to a patient with an AIN in accordance with the relevant guidelines, the main principles did not change during our study's timeline. The protocol included assessment of aldosterone to plasma renin activity ratio when hypertension and/or hypokalemia were present. All patients were subjected to assessment of 24-hour collections of urine for metanephrines. All patients underwent ACTH measurement and a 1 mg overnight DST by administrating 1 mg of dexamethasone (Dekort; Deva, Turkey) between 2300h and 2400h and then taking blood samples for cortisol measurement at the following morning between 0800 h and 0900 h. Evaluation of cortisol secretion status was performed at each follow-up visit. Assessment of 24-hour collections of urine for metanephrines and aldosterone to plasma renin activity ratio was repeated when clinical suspicion was present.

Adrenalectomy was recommended to patients ***(i)*** with overt hormone excess, ***(ii)*** when the cross-sectional imaging at baseline or follow-up could not rule out malignancy or ***(iii)*** significant change increase in size (≥10mm) *and* appearance.

Radiological follow-up was individualized based on the patients characteristics (age, presence of concomitant conditions, symptoms, physical examination findings), radiological characteristics (incidentaloma size at the initial visit, appearance of the incidentaloma, fat content assessed by unenhanced CT and/or magnetic resonance imaging with chemical shift).

Study Participants

The total number of patients in the database was 908 at the time of evaluation. We excluded patients without follow-up data (n=101), patients with pheochromocytomas (n=74), cysts or myelolipomas (n=71), metastasis (n=55), primary hyperaldosteronism (n=49), adrenal Cushing's syndrome (n=50), adrenocortical carcinoma (n=10), ACTH dependent CS and adrenal adenoma (n=7), other/rare (n=3), patients with NFA (n=5) or MACS (n=15) who underwent adrenalectomy without follow-up. We also excluded nine patients (2 NFA, 7 MACS) who underwent adrenalectomy at follow-up due to deteriorations in radiological characteristics and/or accumulation of metabolic problems related with cortisol excess. Pathological examination revealed adrenal adenoma in all subjects.

Statistical Analysis

Statistical analyses were performed using SPSS version 20.0 (SPSS Inc). Distribution of variables was assessed using Kolmogorov Smirnov test. Variables with asymmetric distribution were given as median values and (min-max). Categorical data was presented as percentages and comparisons were performed by Chi-square test. The change in continuous measurements between baseline and follow-up were analysed by Wilcoxon signed rank test for repeated measures. Univariate and Multivariate Logistic Regression Models were employed to establish the predictors of increase in adenoma size and transformation of NFA to MACS at follow-up. Two-tailed tests were used and a significant result was taken as $p < .05$ in all analysis.

Results

Baseline demographic, clinical, hormonal and radiological characteristics were presented in Table 1. Median age of the patients was 55 (21-85) years with a female dominance (73.4%). Median adenoma size was 20 (10-65) mm. Bilateral adenomas were detected in 26.1% of the patients. Extra-adrenal malignancies were observed in 15.6% of the patients. Type 2 diabetes mellitus, arterial hypertension and cardiovascular disease was observed in 25.7%, 49% and 8.1%, respectively.

Table 1: Baseline demographic, clinical, hormonal and radiological characteristics of the patients

Total number of patients, n	467
Age, years	55 (21-85)
Female, % (n)	73.4% (343)
Bilateral adenomas, % (n)	26.1% (122)
Unilateral multiple adenomas, % (n)	3.9% (18)
Adenoma size (mm)	20 (10-65)
Extra-adrenal malignancy, % (n)	15.6 (73)
Diabetes, % (n)	25.7 (120)
Arterial hypertension, % (n)	49 (229)
Cardiovascular disease, % (n)	8.1 (38)
1-mg DST, nmol/l	35.9 (5.5-292.4)
ACTH, pmol/l	3.3 (0-17.3)
MACS, % (n)	29.3 (137)
Follow-up duration, months	60 (12-204)

Continuous variables were presented as median (min-max).
Categorical variables were presented as percent and number.
1mg DST; cortisol level after overnight 1mg dexamethasone suppression test, MACS; mild autonomous cortisol secretion, ACTH; corticotrophin.

Follow-up characteristics in the study group were presented in Table 2. Median follow-up duration was 60 (12-204) months. Follow-up duration was ≥120 months in 16.5%, 60-119 months in 41.5%, 13-59 months in 26.3% and 12 months in 15.6% of the patients. Increase in adenoma size was observed in 36.8% and significant increase (≥10mm) was observed in 4.7% of the patients. Development of overt hormone secretion or adrenocortical carcinoma was not detected while 13 patients with NFA (3.9% of NFA) transformed to MACS and 3 patients with MACS (10.2% of MACS) transformed to NFA at follow-up. Among 13 patients transformed from NFA to MACS, 39% featured ≥10mm increase in adenoma size while this was 4% in patients with stable cortisol secretion level during follow-up (p<.001).

Table 2: Follow-up characteristics in the study group

Total number of patients, n	467
Follow-up duration, months	60 (12-204)
≥ 120 months, % *(n)*	16.5 *(77)*
60-119 months, % *(n)*	41.5 *(194)*
13-59 months, % *(n)*	26.3 *(123)*
12 months, % *(n)*	15.6 *(73)*
Baseline adenoma size, mm	20 (10-65)
Adenoma size (end of follow-up), mm	21 (10-65)*
Stable adenoma size (end of follow-up), % (n)	63.2 *(295)*
Increase in adenoma size (end of follow-up), % (n)	36.8 *(172)*
10 mm or more, % (n)	4.7 *(22)*
5-9 mm, % (n)	11.8 *(55)*
1-4 mm, % (n)	20.3 *(95)*
NFA (baseline), % (n)	70.7 *(330)*
NFA (end of follow-up), % (n)	68.7 *(321)*
MACS (baseline), % (n)	29.3 *(137)*
MACS (end of follow-up), % (n)	25.5 *(119)*
NFA to MACS, % of NFA (n)	3.9 *(13)*
MACS to NFA, % of MACS (n)	10.2 *(14)*
Development of Overt hormone secretion, % (n)	0
Development of Adrenocortical Carcinoma, % (n)	0

Continuous variables were presented as median (min-max). Categorical variables were presented as percent and number. NFA; non-functioning adrenal adenoma, MACS; mild autonomous cortisol secretion. NFA to MACS or MACS to NFA refers to the change in the classification of cortisol autonomy of an adrenal incidentaloma at follow-up.
* $p < .001$ vs baseline (Wilcoxon Signed Rank Test)

Univariate and Multivariate Logistic Regression Models for any increase in adenoma size, ≥10mm increase in adenoma size and transformation of NFA to MACS at follow-up were presented in Table3. Being one year younger at the initial visit (Beta: .051, OR(CI%): 1.2 (1.1-1.3), p< .046), every one-year increase in follow-up (Beta: .171, OR(CI%): 1.3 (1.1-1.4), p=. 004) and transforming from NFA to MACS at follow-up (Beta: 2.352, OR(CI%): 10.5- (2.8-39.2), p< .001) were the independent predictors of an increase ≥10mm in size in multivariate analysis. Likewise, every one-year increase in follow-up duration (Beta: .165, OR(CI%): 1.2 (1-1.4), p=. 025) and ≥10mm increase in adenoma size during follow-up (Beta: 2.295, OR(CI%): 10 (2.7-36.5), p< .001) were the independent predictors of MACS development.

Table 3: Univariate and Multivariate Logistic Regression Models for *(a)* any increase in adenoma size *(b)* 10mm or more increase in adenoma size *(c)* transformation of NFA to MACS at follow-up

(a)	**Univariate Logistic Regression**		**Multivariate Logistic Regression**	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***
Age	1 (0.9-1)	*.114*		
Female	1.3 (0.8 – 1.9)	*.311*		
Malignancy	1.1 (0.7-1.9)	*.612*		
Diabetes	1.3 (0.8-2)	*.254*		
Arterial Hypertension	1.2 (0.8-1.7)	*.372*		
Cardiovascular disease	1.7 (0.8-3.6)	*.165*		
Adenoma size[a]	1.02 (1-1.04)	***.045***	1.02 (1-1.04)	.056
Bilateral adenomas	1.4 (0.9-2.2)	*.131*		
NFA (baseline)	1.2 (0.8-1.8)	*.466*		
MACS (end of follow-up)	1.2 (0.7-1.7)	*.577*		
Follow-up duration[b]	1.2 (1.1-1.2)	***<.001***	1.2 (1.1-1.3)	***<.001***

Univariate and Multivariate Logistic Regression Models for the prediction of any increase in adenoma size during follow-up. In univariate analysis; [a] being 1mm larger at baseline increases the risk of adenoma enlargement by 2%. [b] for every 1 year during follow-up the risk of adenoma enlargement increases by 20%. [NFA]; non-functioning adrenal adenoma, MACS; mild autonomous cortisol secretion

(b)	**Univariate Logistic Regression**		**Multivariate Logistic Regression**	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***
Age[a]	1.1 (1-1.1)	***.017***	1.05 (1-1.1)	***.046***
Female	1.3 (0.7 – 2.4)	*.332*		
Malignancy	1.7 (0.9-3.1)	*.103*		
Diabetes	1.3 (0.4-1.6)	*.611*		
Arterial Hypertension	1.1 (0.6-1.8)	*.661*		
Cardiovascular disease	1.7 (0.8-5.1)	*.307*		
Adenoma size	1 (1-1.01)	*.235*		
Bilateral adenomas	1.1 (0.6-1.9)	*.802*		
NFA (baseline)	1.7 (0.9-3.1)	*.074*		
MACS (end of follow-up)	16.1 (5-54)	***<.001***	10.5 (2.8-39.2)	***<.001***
Follow-up duration[b]	1.3 (1.1-1.4)	***<.001***	1.2 (1.1-1.3)	***<.001***

Univariate and Multivariate Logistic Regression Models for the prediction of 10mm or more increase in adenoma size during follow-up. In univariate analysis; [a] being one year younger increases the risk of ≥10mm enlargement by 10%. [b] every 1 year increase in follow-up is associated with an increase of ≥10mm adenoma enlargement by 30%. Transforming from NFA to MACS at follow-up is the most significant predictor of adenoma enlargement ≥10mm. NFA; non-functioning adrenal adenoma, MACS; mild autonomous cortisol secretion

(c)	**Univariate Logistic Regression**		**Multivariate Logistic Regression**	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***
Age	1.02 (1-1.03)	*.430*		
Female	1.2 (0.5 – 4)	*.727*		
Malignancy	1.03 (0.5-3)	*.964*		
Diabetes	1.3 (0.4-4.2)	*.672*		
Arterial Hypertension	3.3 (0.9-12)	*.07*		
Cardiovascular disease	1.1 (0.2-8.1)	*.953*		
Adenoma size	1.1 (1-1.01)	*.579*		
Bilateral adenomas	1.8 (0.6-5.6)	*.311*		
1mg DST (baseline)	0.5 (0.2-1.2)	*.142*		

(c)	Univariate Logistic Regression		Multivariate Logistic Regression	
Any increase in adenoma size	2.8 (0.9-9)	*.072*		
10mm or more increase in adenoma size	16.1 (5-54.3)	***<.001***	10 (2.7-36.5)	***<.001***
Follow-up duration	1.2 (1.1-1.4)	***.001***	1.2 (1.1-1.4)	***.025***

Univariate and Multivariate Logistic Regression Models for the prediction of transforming from NFA to MACS during follow-up. In univariate analysis; [a] every 1 year increase in follow-up is associated with 20% increase in MACS development. 10mm or more increase in adenoma size is the most significant predictor of MACS development at follow-up. NFA; non-functioning adrenal adenoma, MACS; mild autonomous cortisol secretion

Discussion

In this retrospective cohort study, we showed that, the vast majority of benign adrenal adenomas discovered serendipitously are stable in terms of size and cortisol secretion during follow-up. We did not observe malignant transformation or development of overt hormone excess. Development of MACS is rare and there is a particular interrelation between ≥10mm size increase and transformation from NFA to MACS.

Malignant transformation of an AIN during follow-up is an extremely rare clinical entity. There have been only a few studies reporting the prevalence around %0.2 [6]. Because of the progressive nature of adrenocortical carcinoma, its unequivocal radiological characteristics and association with hormone excess in approximately 60% of the patients [7], probability of a misjudgement at initial diagnosis would be reasonable rather than a malignant transformation during follow-up. Therefore, recent European Society of Endocrinology (ESE) and European Network for the Study of Adrenal Tumours (ENSAT) clinical practice guideline recommends additional imaging, surveillance or surgery unless initial radiological appearance is homogenous and CT Hounsfield Unit value < 10 [4]. Nevertheless, given the ionising radiation dose exposure related with CT and the high cost and low accessibility of MRI, radiological follow-up frequency should be individualized [6].

Development of hormone excess should be discussed in two distinct conditions. First is the development of *overt* hormone excess which has been rarely reported [6,8-10]. An exception for this scenario might be cortisol excess related to primary bilateral macronodular adrenal hyperplasia (PBMAH). In patients with PBMAH and MACS, and particularly in cases with pathogenic germline ARMC5 variants, overt hypercortisolism could develop and closer surveillance is mandatory [11]. Second is the development of MACS at follow-up. Development of MACS has been reported by several investigators with frequencies ranging from 0% to 31% [3-6,8-10,12-15]. Different definitions of MACS and cut-offs for 1 mg DST are the main drawbacks that could explain this particular variation in the development of MACS. In our study, we showed that 3.9% of patients classified as NFA at initial presentation developed MACS at follow-up. We also showed that 10mm or more increase in size is the most significant independent predictor. Our finding endorses hormonal work-up at follow-up in patients with significantly enlarging adrenal adenomas.

In our study, 10mm or more enlargement in adrenal adenomas was noted approximately %5 of the patients. In 63% of the patients the adenoma size was stable. Median follow-up duration was 60 months and median increase in adenoma size was 1mm. In a meta-analysis evaluating over 4000 individuals with AINs [13] the mean tumour growth was 2 mm over a median of 52.8 months of follow-up; only 2.5% of the patients had tumour enlargement of 10mm or more. Adrenal adenomas frequently display stable characteristics in terms of radiological findings at follow-up. Thus, repeated cross-sectional imaging is unnecessary unless new symptoms or hormonal autonomy (overt or MACS) occur.

Clinical follow-up of a patient with an AIN is also important. Radiological interventions are hampered by the exposure to ionizing radiation for CT imaging or the cost and insufficient sources for MRI. In terms of hormonal follow-up, evaluation of cortisol secretion status should be performed at each follow-up visit as transformation from NFA to MACS is not an exceptional finding. Recent findings strongly suggest that MACS is associated with hypertension, glucose intolerance, dyslipidaemia, obesity and cardiovascular risk [16-20]. Additionally, several studies have demonstrated increased cardiometabolic risk in patients with NFA as well [21-26]. These findings emphasize that irrespective of the hormonal or radiological follow-up every AI patient should undergo detailed physical examination, routine laboratory investigations and assessment of cardiovascular risk at certain time intervals.

Conclusion

Incidentally discovered adrenal adenomas feature a stable course in terms of adenoma size and hormonal status. However, given our findings demonstrating an interrelation between adenoma enlargement and MACS development, follow-up radiological and hormonal work-up should be individualized.

Conflict of Interest

None

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