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【 ORIGINAL ARTICLE 】

Clinical Investigation of Adrenal Incidentalomas in Japanese Patients of the Fukuoka Region with Updated Diagnostic Criteria for Sub-clinical Cushing's Syndrome

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Abstract:

Objectives We retrospectively investigated the clinical and endocrinological characteristics of adrenal incidentalomas.

Methods We studied 61 patients who had been diagnosed with adrenal incidentalomas and had undergone detailed clinical and endocrinological evaluations while hospitalized. We used common criteria to diagnose the functional tumors, but for sub-clinical Cushing's syndrome, we used an updated set of diagnosis criteria: serum cortisol ≥1.8 μg/dL after a positive response to a 1-mg dexamethasone suppression test if the patient has a low morning adrenocorticotropic hormone (ACTH) level (<10 pg/mL) and a loss of the diurnal serum cortisol rhythm.

Results Of the 61 patients, none (0%) had malignant tumors, 8 (13.1%) had pheochromocytoma, and 15 (24.6%) had primary aldosteronism; when diagnosed by our revised criteria, 13 (21.3%) had cortisol-secreting adenomas (Cushing's syndrome and sub-clinical Cushing's syndrome), and 25 (41.0%) had non-functional tumors. Compared with the non-functional tumor group, the primary aldosteronism group and the cortisol-secreting adenoma group were significantly younger and had significantly higher rates of hypokalemia, whereas the pheochromocytoma group had significantly larger tumors and a significantly lower body mass index.

Conclusion Our study found a larger percentage of functional tumors among adrenal incidentalomas than past reports, partly because we used a lower serum cortisol level after a dexamethasone suppression test to diagnose sub-clinical Cushing's syndrome and because all of the patients were hospitalized and could therefore receive more detailed examinations. Young patients with hypokalemia or lean patients with large adrenal tumors warrant particularly careful investigation.

Key words: adrenal incidentaloma, pheochromocytoma, primary aldosteronism, Cushing's syndrome, sub-clinical Cushing's syndrome

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Introduction

Adrenal incidentalomas are defined as adrenal tumors that are unexpectedly discovered in imaging examinations (1, 2); their incidence has increased with advances in imaging technology (2, 3). Several studies have shown variable frequency in types of functional tumors among adrenal incidentalomas (4-9), including two studies in Japan. Ichijo and Ueshiba reported that the frequencies for adrenal incidentaloma were as follows: non-functional adenomas, 50.8%; pheochromocytoma, 8.5%; primary aldosteronism (PA), 5.1%; cortisol-secreting adenoma [Cushing's syndrome (CS) or sub-clinical Cushing's syndrome (SCS)], 10.5%; and others [including non-functional tumors (NFTs), except for non-functional adenomas], 25.1%, among 3,678 cases (8). Recently, Tabuchi et al. also reported frequencies for adrenal incidentaloma as follows: NFTs, 73.3%; pheochromocytoma, 4.7%; PA, 9.3%; cortisol-secreting adenoma (CS or SCS), 11.4%; and SCS with PA, 1.3%, among 150 cases (9).

Notably, both of these investigators used a set of diagnostic criteria for SCS widely applied in Japan: serum cortisol ≥3.0 μg/dL after a 1-mg dexamethasone suppression test (DST). However, the American Endocrine Society suggests using serum cortisol ≥1.8 μg/dL after a 1-mg DST (10) be used as the cut-off value, and Akehi et al. reported that serum cortisol ≥1.8 μg/dL after a 1-mg DST was better for diagnosing SCS in Japanese patients than other criteria (11). We therefore used cortisol ≥1.8 μg/dL after a 1-mg DST for a diagnosis, provided a patient had both a lower morning adrenocorticotropic hormone (ACTH) level (<10 pg/mL) and loss of diurnal serum cortisol rhythm, and then re-evaluated the percentage of functional tumors among adrenal incidentalomas. All patients in this study had been hospitalized, which facilitated thorough clinical and endocrinological investigations for adrenal incidentalomas.

We herein report the findings of an analysis of adrenal incidentalomas using updated criteria for SCS with highly detailed evaluations. We also investigated commonly available clinical factors that differ between patients with functional tumors and those with NFTs.

Materials and Methods

Subjects

Our study included 61 individuals who were found to have adrenal incidentalomas at Fukuoka University Chikushi Hospital or at other hospitals first before being introduced to Fukuoka University Chikushi Hospital from April 2014 to March 2017. Adrenal incidentalomas were detected incidentally on imaging examinations performed for the checkup of non-endocrine diseases, a general checkup, or abdominal symptoms. All of them had been hospitalized and undergone endocrinological evaluations and laboratory testing, and we investigated the data. The study protocol was approved by the Ethics Review Committee of Fukuoka University (Japan) and performed according to the principles of the Declaration of Helsinki.

Methods

We collected data on the age, sex, tumor size and laterality, medical history, physical examination findings, laboratory tests, and endocrinological evaluations for all patients. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or use of antihypertensive drug. Diabetes mellitus was defined as any combination of fasting blood sugar ≥126 mg/dL, random blood sugar ≥200 mg/dL, HbA1c ≥6.5%, or the use of antidiabetic agents. Dyslipidemia was defined as any combination of total cholesterol level ≥220 mg/dL, low-density lipoprotein-cholesterol ≥ 140 mg / dL, high-density lipoprotein-cholesterol <40 mg/dL, triglyceride ≥150 mg/dL, or the use of lipid-lowering drugs.

Functional tumors

PA was diagnosed after captopril-challenge tests, saline-loading tests, and upright furosemide-loading tests among patients whose plasma aldosterone concentration (pg/mL)/plasma renin activity (ng/mL/h) >200, as described by Nishikawa et al. (12).

Pheochromocytoma was diagnosed by the combination of elevated plasma catecholamine levels (3 times more than normal range), elevated urinary catecholamine levels (3 times more than normal range), elevated 24-hour urinary catecholamine metabolites (3 times more than normal range), and a positive accumulation on ^{123}I-metaiodobenzylguanidine scintigraphy (13, 14).

CS was diagnosed by (a) the presence of Cushing's sign; (b) a low morning ACTH level (<5 pg/mL) instead of normal or high levels; (c) loss of diurnal serum cortisol rhythm; (d) a low serum dehydroepiandrosterone-sulfate (DHEA-S) level (with respect to the patient's age and sex); (e) a high urinary free cortisol level; (f) a unilateral uptake of ^{131}I-adosterol on adrenal scintigraphy; and (g) autonomic cortisol secretion confirmed by a 1-mg/8-mg DST.

SCS was diagnosed by (a) a lack of Cushing's sign; (b) a normal morning serum cortisol levels at morning; (c) a low morning ACTH level (<10 pg/mL); (d) loss of diurnal serum cortisol rhythm; (e) a low serum DHEA-S level (with respect to the patient's age and sex); (f) a unilateral uptake of ^{131}I-adosterol on adrenal scintigraphy; (g) transient adrenal insufficiency or atrophy of the residual normal adrenal after removing the adrenal tumor, and (h) autonomic cortisol secretion confirmed by a 1-mg DST (15).

As for DST, serum cortisol levels ≥5.0 μg/dL after 1- and 8-mg DSTs were indicative of a diagnosis of CS. To diagnose SCS, serum cortisol levels ≥3.0 μg/dL after a 1-mg DST are the most widely used criterion for SCS in Japan. However, we adopted serum cortisol levels ≥1.8 μg/dL after a 1-mg DST as the criterion for SCS, as suggested by the American Endocrine Society and reported to be suitable for

Table 1. Clinical Characteristics of the Patients with Adrenal Incidentalomas.

	n=61
Age (years)	62.9±10.9
Male/Female	25/36
SBP (mmHg)	129.0±18.5
DBP (mmHg)	76.3±11.9
BMI (kg/m^2)	23.3±4.5
FBS (mg/dL)	106.3±31.6
HbA1c (%)	6.09±1.2
LDL-cholesterol (mg/dL)	114.2±37.5
HDL-cholesterol (mg/dL)	56.9±17.1
Triglyceride (mg/dL)	113.9±60.2
AST (U/L)	25.9±15.6
ALT (U/L)	23.7±13.6
γ-GTP(U/L)	46.3±48.0
eGFR (mL/min/1.73m^2)	76.2±20.6
Na (mmol/L)	140.2±3.1
K (mmol/L)	3.81±0.46
Cl (mmol/L)	106.0±3.1
Medical treatment for hypertension	36 (59.0 %)
Medical treatment for diabetes mellitus	11 (18.0 %)
Medical treatment for dyslipidemia	16 (26.2 %)
Past history of cardiovascular disease	5 (8.20 %)
Past history of cerebrovascular disease	2 (3.28 %)
Past history of heart failure (acute and/or chronic)	3 (4.92 %)
Tumor laterality (right/left)	23/38
Tumor size (mm)	21.8±10.8

Data are shown as means±standard deviation (SD). LDL: low-density lipoprotein, HDL: high-density lipoprotein, eGFR: estimated glomerular filtration rate

Japanese patients by Akehi et al. provided patients have both a low morning ACTH level (<10 pg/mL) and loss of diurnal serum cortisol rhythm (10, 11, 16). Serum cortisol levels were measured using RIA kits (Immunotech, Marseilles, France).

Statistical analyses

Data were expressed as the means ± standard deviation. The significance of differences between means was estimated by Student's *t*-test. $p<0.05$ was considered significant.

Results

Table 1 shows the 61 patients' clinical characteristics. Their mean age was 62.9±10.9 years (range: 43-84 years); 25 patients (41.0%) were men, and 36 (59.0%) were women. All patients were hospitalized and received detailed examinations.

Of the 61 adrenal incidentalomas, 33 (54.1%) were detected at a checkup for other diseases, 23 (37.1%) were detected at general check-up, and 16 (26.2%) were detected based on abdominal symptoms. A total of 23 (37.7%) were found in the right adrenal glands, and 38 (62.3%) were found in the left; their mean size was 21.8±10.8 mm, and 59 were detected by computed tomography (96.7%) and 2 by ultrasonography (3.3%).

Among the patients, 16 had diabetes mellitus, 39 had hypertension, and 16 had dyslipidemia; 21 had hypokalemia (K<3.8 mmol/L). Their other endocrinological findings are shown in Table 2. No patients in this study were found to have adrenocortical carcinoma, malignant lymphoma, or metastatic adrenal tumor; 8 (13.1%) had pheochromocytoma, and 15 (24.6%) had PA. Among the 38 other patients, our modified criteria for serum cortisol after a 1-mg DST found that 13 patients had cortisol-secreting adenomas (CS: 3 patients and SCS: 10 patients), and 25 (41.0%) had NFTs, compared with 8 (13.1%) cortisol-secreting adenomas (CS: 3 patients and SCS: 5 patients) and 30 (49.2%) NFTs when assessed with the higher criterion more commonly used in Japan. For the patients diagnosed with SCS, no significant differences were noted between patients diagnosed by the updated criteria for SCS and those diagnosed by the criteria commonly used in Japan for sex (men: 20% vs. 20%, p=1.000), age (58.8±9.6 vs. 58.8±7.8 years, p=1.000), tumor laterality (right: 60% vs. 40%, p=0.580), tumor size (18.0±5.7 vs. 17.8±2.3 mm, p=0.954), value of morning serum cortisol (11.6±1.2 vs. 13.7±1.4 μg/dL, p=0.954), and complications (hypertension: 60% vs. 80%, p=0.545; diabetes mellitus: 40% vs. 60%, p=0.580; dyslipidemia: 20% vs. 20%, p=1.000; hypokalemia: 80% vs. 60%, p=0.545), as shown in Table 3.

Twenty-two patients underwent surgery (all laparoscopically) including all 8 patients with pheochromocytoma (100%), 4 (26.7%) with PA, 7 (53.8%) with cortisol-secreting adenomas (CS or SCS), and 3 (12.0%) with NFTs. All pre-surgical diagnoses were accurate histopathologically.

We also investigated whether or not functional adrenal incidentalomas could be predicted based on commonly available data and symptoms, as shown in Table 4. We found no significant differences between the functional tumor group and NFT group with respect to the age, sex, laterality, hypertension, diabetes mellitus, or dyslipidemia. However, the functional tumor group had a significantly higher rate of hypokalemia than did the NFT group (34.4% vs. 16.0%, p=0.011); in particular, the NFT group had a significantly lower hypokalemia rate (16.0%) than did the PA group (71.4%, p=0.001) or the cortisol-secreting adenoma (CS or SCS) group (53.8%, p=0.014). The NFT group also had a significantly higher mean age (66.0±10.1 years) than did the PA group (59.4±8.7 years, p=0.049) and the cortisol-secreting adenoma (CS or SCS) group (58.0±9.2 years, p=0.043). Compared with the NFT group, the pheochromocytoma group had significantly larger tumors (35.8±15.4 vs. 21.0±9.1 mm, p=0.039) and lower BMIs (20.6±2.9 vs. 24.6±4.4, p=0.027).

Discussion

The prevalence of adrenal incidentalomas has increased with recent advances in imaging technology (2, 3). Several studies have shown various frequencies of functional tu-

Table 2. Diagnose of Adrenal Incidentalomas with Endocrinological Investigation.

	Number (%)
Pheochromocytoma	8 (13.1%)
Primary aldosteronism	15 (24.6%)
Prevalence with our criteria of sub-clinical Cushing's syndrome.	
Cortisol secreting adenoma	13 (21.3%)
Cushing's syndrome	3 (4.9%)
Sub-clinical Cushing's syndrome	10 (16.4%)
Non-functioning tumor	25 (41.0%)
Prevalence with the criteria of sub-clinical Cushing's syndrome widely used in Japan.	
Cortisol secreting adenoma	8 (13.1%)
Cushing's syndrome	3 (4.9%)
Sub-clinical Cushing's syndrome	5 (8.2%)
Non-functioning tumor	30 (49.2%)

The dissimilarity between our criteria of sub-clinical Cushing's syndrome and the criteria widely used in Japan was the positive value of patients' serum cortisol levels after 1 mg dexamethasone suppression test (DST). In our criteria, patients' serum cortisol levels ≥ 1.8 μg/dL after 1 mg DST were positive for diagnosis of sub-clinical Cushing's syndrome if satisfying both lower morning ACTH level instead of normal or high levels, and loss of diurnal serum cortisol rhythm. In the criteria widely used in Japan, patients' serum cortisol levels ≥3.0 μg/dL after 1 mg DST were positive for diagnosis of sub-clinical Cushing's syndrome.

Table 3. Comparison of Patients Diagnosed by Updated Criteria for Sub-clinical Cushing's Syndrome and Those Diagnosed by Criteria Widely Used in Japan.

Patients diagnosed as sub-clinical Cushing's syndrome by the criteria of widely used in Japan.						
Sex	Age (years)	Tumor laterality	Tumor size (mm)	Morning serum cortisol (μg/dL)	Serum cortisol after 1mg DST (μg/dL)	Complications
F	76	right	8	11.3	8.3	hypokalemia
F	53	left	26	10.9	6.2	hypertension
F	61	right	17	14.2	6.1	diabetes mellitus, dyslipidemia, hypokalemia
F	44	right	16	11.1	3.2	hypertension, hypokalemia
M	60	left	23	10.6	5.5	hypertension, diabetes mellitus, hypokalemia
Patients diagnosed as sub-clinical Cushing's syndrome only by updated criteria						
Sex	Age (years)	Tumor laterality	Tumor size (mm)	Morning serum cortisol (μg/dL)	Serum cortisol after 1mg DST (μg/dL)	Complications
F	55	left	16	12.2	1.9	hypokalemia
F	69	right	20	12.1	1.8	hypertension
F	59	right	14	14.7	2.3	hypertension, diabetes mellitus, dyslipidemia
M	45	left	18	16.1	1.9	hypertension, diabetes mellitus, hypokalemia
F	66	left	21	12.8	1.9	hypertension, diabetes mellitus, hypokalemia

There was not significant difference between patients diagnosed only by updated criteria for SCS and those diagnosed by criteria commonly used in Japan at the point of sex, age, tumor laterality, tumor size, value of morning serum cortisol, and complications (each $p>0.05$). The significance of differences between means was estimated by the Student's *t*-test. $p<0.05$ was considered significant.

mors (4-9), including two recent studies in Japan (8, 9). In the present study, we investigated all patients with adrenal incidentalomas using the most recent criteria, which included a lowered cut-off point for serum cortisol levels following a 1-mg DST for diagnosing SCS. The American Endocrine Society suggested a serum cortisol level ≥1.8 μg/dL after a 1-mg DST be used to diagnose SCS, although a serum cortisol level ≥3.0 μg/dL is widely used in Japan (10). Of note, Akehi et al. reported a serum cortisol ≥1.8 μg/dL after a 1-mg DST to be a better diagnostic standard for SCS in Japanese patients than the widely used criterion (11), and in its most recently-modified guideline, the Japan Endocrine Society also recommended this lower cut-off level be used for Japanese patients meeting the following conditions: no Cushing's sign, a normal basal serum cortisol level, a low morning ACTH level (<10 pg/mL), and loss of diurnal se-

Table 4. Clinical Characteristics of Patients with Each Adrenal Incidentalomas.

	Non-functional tumor	Functional tumor	Pheochromocytoma	Primary aldosteronism	Cortisol secreting adenoma
Number	25 (41.0 %)	36 (59.0%)	8 (13.1%)	15 (24.6%)	13 (21.3%)
Age (years)	66.0±10.1*#	60.7±10.8	67.3±13.8	59.4±8.7*	58.0±9.2#
Male (%)	40.0	41.6	50.0	57.1	23.0
BMI	24.6±4.4$	22.3±4.4	20.6±2.9$	22.4±2.5	23.5±6.1
Hypertension (%)	55.0	69.4	37.5	78.5	84.6
Diabetes mellitus (%)	20.0	27.8	37.5	7.1	53.8
Dyslipidemia (%)	25.0	27.8	0.0	21.4	46.1
Hypokalemia (%)	16.0§&+	47.2§	0.0	71.4&	53.8+
Tumor size (mm)	21.0±9.1¶	22.1±12.0	35.8±15.4¶	22.4±2.5	19.1±6.9
Rate of operation (%)	3 (12.0 %)	19 (52.8 %)	8 (100 %)	4 (26.7 %)	7 (53.8 %)

Data are shown as means±standard deviation (SD). The functioning tumor group had significantly more hypokalemia than the non-functional tumor (NFT) group ($p=0.011). In detail, patients with primary aldosteronism and cortisol secretingadenomas had significantly more hypokalemia (&p=0.014 and +p=0.001) and were significantly younger (*p=0.049 and #p=0.043) than the NFT group. The pheochromocytoma group had significantly larger tumors (¶p=0.039) and significantly lower BMI ($p=0.026) than the NFT group. The significance of differences between means was estimated by the Student's*t*-test. p<0.05 was considered significant. BMI: body mass index

rum cortisol rhythm (17). As our study used this lower serum cortisol criterion to diagnose SCS, in contrast to previously reported papers that used the higher cut-off level, our rates of functional tumors differed from those described in the literature. Furthermore, given that no significant difference were noted between the patients diagnosed using the updated criteria for SCS and those diagnosed using the criteria commonly used in Japan with regard to the sex, age, tumor laterality, tumor size, baseline value of serum cortisol, and complications, we feel that the updated criteria for SCS were useful for the diagnosis of SCS.

Another reason our study showed a higher functional tumor rate than past reports (including the two reports in Japanese patients) is that all patients were hospitalized, which facilitated more detailed medical investigations. For instance, in the pheochromocytoma group (n = 8), 3 patients had normal plasma catecholamine levels but high urinary catecholamine levels and 24-hour urinary catecholamine metabolites, showing positive results on ^{123}I-metaiodobenzylguanidine scintigraphy. We believe that these findings led to a higher functional tumor rate than was seen in earlier reports.

We also tried to identify commonly available data parameters that could be used to tell the difference between functional and NFTs in cases of adrenal incidentaloma. Compared with the NFT group, the PA group and cortisol-secreting adenoma (CS or SCS) group were significantly younger (p=0.049 and 0.043, respectively) and had a significantly higher incidence of hypokalemia (p=0.014 and 0.001, respectively). In addition, compared with the NFT group, the pheochromocytoma group had significantly larger tumors (p=0.039) and a lower BMI (p=0.026). Pheochromocytoma, cortisol-secreting adenomas (CS or SCS), and PA are commonly thought to cause hypertension and diabetes mellitus and cortisol-secreting adenoma (CS and SCS) to cause dyslipidemia (18-22). However, in our study, we found no significant difference in the incidence of hypertension, diabetes mellitus, or dyslipidemia between the NFT group and patients with functional tumors, including pheochromocytoma, cortisol-secreting adenoma (CS or SCS), and PA. Two previous studies have shown that NFTs were complicated by glucose intolerance, hypertension, and dyslipidemia (23, 24). The reason for this is not entirely clear, but our findings were similar. The mechanical relationships between NFTs and increased glucose intolerance and hypertension warrant further study. However, hypertension, diabetes mellitus, and dyslipidemia are not apparently useful for predicting whether an adrenal incidentaloma is functional or non-functional.

Our study was limited by the relatively small number of cases. Future studies should include larger subject populations.

In conclusion, our study showed a higher ratio of functional tumors among adrenal incidentalomas than past reports. Adrenal incidentalomas should be investigated carefully; patients may require hospitalization to facilitate an adequate examination and specialized evaluations from endocrinologists. PA and cortisol-secreting adenomas (CS or SCS) should be considered in the differential diagnosis for young patients with hypokalemia, and pheochromocytoma should be considered for lean patients with large adrenal tumors.

Author's disclosure of potential Conflicts of Interest (COI).

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