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Professor Special Lecture: 74th Annual Meeting of the Medical Society of Toho University

Review Article

Adrenal Incidentaloma in Japan

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ABSTRACT: This paper aims to evaluate the epidemiologic and clinical characteristics of incidentally discovered adrenal masses, referred to as adrenal incidentalomas, in Japan. The original study had been carried out as a project of a research proposed on behalf of the Japanese Ministry of Health, Labour and Welfare, from 1999 to 2004. This nationwide multicenter study has examined clinically diagnosed 3,672 cases of adrenal incidentalomas, involving 1,874 males and 1,738 females, with mean age 58.1 ± 13.0 years (mean ± SD). The mean nodule size of adrenal incidentaloma based on computed tomography (CT) was 3.0 ± 2.0 cm. Compared to non-functioning adenomas, tumor diameters were found to be significantly larger in adrenocortical carcinomas, pheochromocytomas, cortisol-producing adenomas, myelolipomas, metastatic tumors, cysts, and ganglioneuromas ($p < 0.01$). Endocrinological evaluations demonstrated that 50.8% of the total adrenal incidentalomas were non-functioning adenomas, while 10.5%, including 3.6% with subclinical Cushing's syndrome, were reported as cortisol-producing adenomas, 8.5% as pheochromocytomas, and 5.1% as aldosterone-producing adenomas. Adrenocortical carcinomas were accounted for 1.4% (50 cases) among our series of adrenal incidentalomas. In conclusion, while almost 50% of adrenal incidentalomas are non-functional adenomas, we must exercise great caution as adrenal incidentalomas also include pheochromocytomas or adrenocortical carcinomas, because they may be asymptomatic.

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KEYWORDS: adrenal incidentaloma, non-functioning adenoma, adrenocortical carcinoma

Introduction

The incidence of clinically inapparent and incidentally discovered adrenal masses, called adrenal incidentaloma, has seen a significant increase over the last two decades as a result of the widespread use and technical improvement of abdominal imaging devices, including ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI).[1] The current prevalence of adrenal incidentaloma, which is defined as an adrenal mass occasionally and unexpectedly discovered by abdominal imaging procedures performed for non-adrenal-related reasons, is approximately 1% to 5% in abdominal CT scan series,[2-4] and most cases are discovered before they become severe or critical. However, this rate might be an underestimate. In fact, the incidence of adrenal nodules at autopsy is as high as 32% among patients who had no evidence of adrenal disease prior to their deaths.[3-5] Many

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adrenal incidentalomas, even if they are diagnosed as non-functioning adenomas, are associated with metabolic syndrome.[6] In addition, adrenocortical carcinoma is rare, with an estimated yearly incidence of 0.5 to 2 per 1×10^6 patients,[7] although its prevalence is as high as 25% among patients with adrenal incidentaloma.[8] The prognosis of adrenocortical carcinoma is generally poor, and the overall 5-year survival rate after diagnosis is 7% to 65%.[9] Therefore, once an adrenal incidentaloma is detected, it raises challenging questions for physicians and their patients; thus, a series of diagnostic evaluations should be performed to determine whether the lesion is hormonally hyperactive or non-functioning, whether it is malignant or benign,[10] and whether the nodule is growing in size or not, although these evaluations are usually very demanding. As a consequence, adrenal incidentalomas have become a common clinical problem.[11]

In this study, we have performed a nationwide multicenter study as a project of the Research Committee on Disorders of Adrenal Hormones, proposed on behalf of the Japanese Ministry of Health, Labour and Welfare, from 1999 to 2004. We present here the overview of a 5-year nationwide survey, which included more than 3,600 patients with adrenal incidentalomas in Japan. A long-term follow-up study was conducted as the second study from 2013 to 2016.

The Definition of Adrenal Incidentaloma

We defined "adrenal incidentaloma" as a clinically inapparent mass, which is discovered accidentally through imaging procedures performed for non-adrenal-related reasons, regardless of complications such as hypertension or diabetes, which could be caused by the adrenal mass.

Study Designs

Our study contains two nationwide multicenter studies. The first study was conducted from 1999 to 2004 as a cross-sectional and 5-year follow-up study, whereas the second study was performed from 2013 to 2016 as a long-term follow-up study. A nationwide multicenter study of adrenal incidentaloma by the Research Committee on Disorders of Adrenal Hormones was firstly proposed and performed on behalf of the Japanese Ministry of Health, Labour and Welfare from 1999 to 2004 as the first study. Since more than 10 years had passed since the above first nationwide study of adrenal incidentaloma, a long-term follow-up study of adrenal incidentaloma was proposed and conducted by the Research Committee on Disorders of Adrenal Hormones on behalf of the Japanese MHLW from 2013 through 2016 as the second study. This report of a nationwide multicenter survey on adrenal incidentaloma is a 5-year project that started in 1999, wherein 1,014 hospitals with more than 200 beds, identified based on the official medical facilities list, were annually requested to review all of their cases of adrenal incidentaloma since 1995. All questionnaires were individually checked for inconsistencies, such as clinical signs of hormonal hypersecretion or multiplicate inclusion of the same patients, before statistical analysis; in total, 3,672 cases were included in this study.

General Background of Patients

In this study, 3,672 cases were finally included. There was no significant difference in terms of gender in the included patients, with 1,874 males (51.0%), 1,738 females (47.3%), and 60 not reported cases (1.6%), aged between 6 months and 92 years (mean ± SD, 58.0 ± 13.0 years), taking part in the study. The numbers of each diagnostic technique represent the final main diagnostic imaging technique. Median nodule size was 2.5 cm (range, 0.5-30, mean ± SD, 3.0 ± 2.2 cm), the mean ± SD of body mass index (BMI) was 23.5 ± 3.8 kg/m^2 (range, 12.1-39.9), and the mean ± SD of HOMA-R was 2.1 ± 1.4 (range, 0.4-7.2). Hypertension, diabetes, and obesity were observed in 24.1%, 12.2%, and 12.0% of patients, respectively. In total, 933 cases of patients including adrenalectomy performed were followed up, and their median follow-up period was 2 years (range, 1-19).

The Prevalence of Each Nodule Type and Patients' Background (Fig. 1)

The clinically diagnosed classification and prevalence of each nodule among the 3,672 cases were as follows: 1,866 non-functioning adenomas (50.8%); 386 cortisol-producing adenomas, including patients with subclinical Cushing's syndrome (SCS, 10.5%); 312 pheochromocytomas (8.5%); 187 aldosterone-producing adenomas (5.1%); 147 hyperplasias (4.0%); 140 metastatic tumors (3.8%); 132 myelolipomas (3.6%); 84 cysts (2.3%); 59 ganglioneuromas (1.6%); 51 adrenocortical carcinomas (1.4%); 7 androgen-producing adenomas (0.2%); and 22 pseudo-adrenal masses (0.6%), respectively.

Cortisol-producing adenomas and aldosterone-produc-

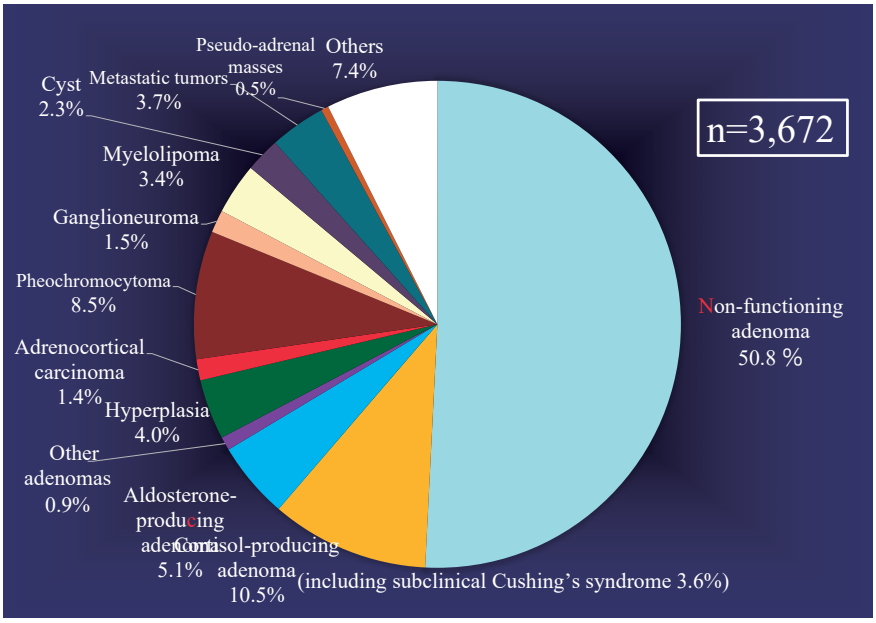

Fig. 1 The classification and prevalence of adrenal incidentaloma

ing adenomas were determined to be significantly more common in females ($p<0.0001$) compared to non-functioning adenomas. Patients with cortisol-producing adenomas, aldosterone-producing adenomas, androgen-producing adenomas, pheochromocytomas, ganglioneuromas, and pseudo-adrenal masses were significantly younger ($p<0.0001$), and patients with metastatic tumors were significantly older ($p<0.0001$), than those with non-functioning adenomas.

Nodule Sizes and Growth Speeds of Adrenal Incidentaloma Types

Compared to non-functioning adenomas, tumor diameters were significantly larger in adrenocortical carcinomas, pheochromocytomas, cortisol-producing adenomas, myelolipomas, metastatic tumors, cysts, and ganglioneuromas ($p<0.01$), while they were significantly smaller in aldosterone-producing adenomas ($p<0.001$).

In total, 894 of the 933 cases, excluding those cases without nodule sizes in follow-up, were followed up annually for changes in nodule sizes, with 37.0% and 20.1% of patients showing enlargement or shrinkage of >0.5 cm during follow-up, respectively. The ratio of nodules increasing in size by >0.5 cm and the % annual increase for each nodule type were 36.5% (230 of 631) and 2.8 ± 12.2% for non-functioning adenomas; 29.5% (13 of 44) and 2.7 ± 14.4% for cortisol-producing adenomas; 14.3% (2 of 14) and 2.5 ± 12.6% for aldosterone-producing adenomas; 31.8% (7 of 22) and 3.8 ± 14.3% for hyperplasias; 50.0% (3 of 6) and 12.6 ± 15.0% for adrenocortical carcinomas; 50.0% (11 of 22) and 4.9 ± 11.1% for pheochromocytomas; 45.2% (14 of 31) and 1.2 ± 8.4% for myelolipomas; 70.8% (17 of 24) and 42.2 ± 76.2% for metastatic tumors; 40.9% (9 of 22) and 13.4 ± 36.0% for cysts; and 50.0% (1 of 2) and 12.5 ± 17.7% for ganglioneuromas, respectively. The ratio of nodules with increased sizes was significantly higher in patients with metastatic tumors than in those with non-functioning adenomas ($p<0.005$), and only metastatic tumors and cysts showed significantly faster growth in their sizes than non-functioning adenomas ($p<0.0001$, $p<0.01$; respectively).

Conclusion

While almost 50% of adrenal incidentalomas are non-functional adenomas, we must still exercise great caution as adrenal incidentalomas include pheochromocytomas or adrenocortical carcinomas, because they may be asymptomatic. Our data indicate that a conservative management is appropriate in the majority of adrenal incidentalomas. However, the prevalence of adrenocortical carcinomas among adrenal incidentalomas and the frequency of nodules with hormonal hypersecretion seem to be comparatively high; therefore, careful and cost-effective follow-up and a decision for surgery at the appropriate time are recommended, especially in patients with a potentially higher risk of malignancy and/or pro-

gressive hypersecretion.

Conflicts of interest: None declared

References

1) Brunt LM, Moley JF. Adrenal incidentaloma. World J Surg. 2001; 25: 905-13.
2) Mantero F, Arnaldi G. Management approaches to adrenal incidentalomas. A view from Ancona, Italy. Endocrinol Metab Clin North Am. 2000; 29: 107-25, ix.
3) Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016; 175: G1-G34.
4) Young WF Jr. Clinical practice. The incidentally discovered adrenal mass. N Engl J Med. 2007; 356: 601-10.
5) Jenkins PJ, Chew SL, Lowe DG, Reznek RH, Wass JA. Adrenocorticotrophin-independent unilateral macronodular adrenal hyperplasia occurring with myelolipoma: an unusual cause of Cushing's syndrome. Clin Endocrinol (Oxf). 1994; 41: 827-30.
6) Midorikawa S, Sanada H, Hashimoto S, Suzuki T, Watanabe T. The improvement of insulin resistance in patients with adrenal incidentaloma by surgical resection. Clin Endocrinol (Oxf). 2001; 54: 797-804.
7) Ng L, Libertino JM. Adrenocortical carcinoma: diagnosis, evaluation and treatment. J Urol. 2003; 169: 5-11.
8) Kloos RT, Gross MD, Francis IR, Korobkin M, Shapiro B. Incidentally discovered adrenal masses. Endocr Rev. 1995; 16: 460-84.
9) Miller BS, Else T, AACE Adrenal Scientific Committee. Personalized care of patients with adrenocortical carcinoma: a comprehensive approach. Endocr Pract. 2017; 23: 705-15.
10) Grumbach MM, Biller BM, Braunstein GD, Campbell KK, Carney JA, Godley PA, et al. Management of the clinically inapparent adrenal mass ('incidentaloma'). Ann Intern Med. 2003; 138: 424-9.
11) Mantero F, Terzolo M, Arnaldi G, Osella G, Masini AM, Alì A, et al. A survey on adrenal incidentaloma in Italy. Study Group on Adrenal Tumors of the Italian Society of Endocrinology. J Clin Endocrinol Metab. 2000; 85: 637-44.

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Education and Training

1977-1983 Toho University School of Medicine

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Appointments

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