

Clinical investigation of pituitary incidentalomas: A two-center study

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Summary

Recent advances in imaging technology resulted in an increase in pituitary incidentalomas (PIs) detection. PIs were reported to be present in 1.6% persons with magnetic resonance imaging of the brain. Whereas, there were few studies about PIs with detailed investigation. We aimed to investigate the clinical and endocrinological characteristics of PIs. We evaluated 65 patients diagnosed with PIs who underwent detailed clinical and endocrinological evaluations. Of the 65 patients, 33 (50.8%) had non-functional pituitary adenomas (NFPAs), 11 (16.9%) had Rathke's cleft cysts (RCCs), 7 (10.8%) had functional pituitary adenomas (FPAs), 6 (9.2%) had benign extra-pituitary tumors (BEPTs), and 8 (12.3%) had malignant tumors (MTs). Compared with patients with NFPAs, those with MTs were significantly younger and had a significantly lower body mass index, lower prevalence of hypertension, and lower prevalence of dyslipidemia. Patients with MTs had significantly higher prevalence of central diabetes insipidus than those with NFPAs. In addition, patients with NFPAs had significantly higher prevalence of pituitary apoplexy than those with FPAs, BEPTs, and MTs. In conclusion, our study demonstrated clinical and endocrinological characteristics of PIs. Highly detailed clinical and endocrinological investigations should be performed for PIs. In addition, MTs should be considered in the differential diagnosis for young and lean patients with central diabetes insipidus.

Keywords: Pituitary incidentaloma, hormonal deficiency, pituitary apoplexy

1. Introduction

Pituitary incidentalomas (PIs) are tumors of the pituitary gland discovered unexpectedly upon imaging that are

not due to symptoms related specifically to the lesion (e.g., visual loss) or a clinical manifestation of hormonal disorders (1). Vernooij and colleagues reported analysis of patient with magnetic resonance imagings of the brain showed PIs were present in 1.6% persons (2). The previous autopsy investigations also showed the prevalence of PIs were 2.7-24.0 % (3-5). Whereas, adrenal incidentalomas, the same endocrine incidental tumors as PIs, have been investigated in several studies (6-9), even though their prevalence investigated by autopsy were reported to be lower than that of PIs (1.1-5.0 %) (10-12). However, few studies have focused on PIs (2,13,14).

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The Endocrine Society (Washington, DC, USA) produces guidelines for the clinical management for several endocrine diseases including PIs authored by Freda and colleagues (1). They recommended that patients with PIs undergo thorough history-taking and a complete physical examination, including evidence of asymptomatic hormonal disorders.

Here, we demonstrate the findings of an analysis of the clinical and endocrinological characteristics of PIs with highly detailed evaluations in two university hospitals.

2. Materials and Methods

2.1. Ethical approval of the study protocol

The study protocol was approved by the Ethics Review Committees of Fukuoka University (Fukuoka, Japan) and Yamagata University (Yamagata, Japan). Written informed consent was obtained from the patients for participation in the study. The study was carried out according to the principles of the Helsinki Declaration.

2.2. Subjects

The study cohort comprised 65 individuals found to have PIs at Yamagata University Hospital or Fukuoka University Chikushi Hospital (or individuals with PIs detected at other hospitals and who were then transferred to these two institutions) from April 2015 to March 2018.

PIs were diagnosed with the criteria: detected incidentally upon imaging examinations undertaken for monitoring of non-endocrine diseases; general health status; various symptoms not considered to have a relationship with the lesion, defined by The Endocrine Society produces guidelines (1). All study participants underwent endocrinology evaluations and laboratory tests.

2.3. Methods and disease definitions

We collected data on age, sex, tumor diameter, medical history, physical examination, 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 drugs. Diabetes mellitus was defined as any combination of: fasting plasma glucose ≥ 126 mg/dL; random plasma glucose ≥ 200 mg/dL; glycosylated hemoglobin $\geq 6.5\%$; or use of antidiabetic agents. Dyslipidemia was defined as any combination of total cholesterol ≥ 220 mg/dL; low-density lipoprotein-cholesterol ≥ 140 mg/dL; high-density lipoprotein-cholesterol < 40 mg/dL; triglyceride ≥ 150 mg/dL; or use of lipid-lowering drugs.

2.4. Functional pituitary adenomas

The diagnosis of functional pituitary adenomas (FPAs) was performed in accordance with previous reports (15-19). In detail, a growth hormone (GH)-producing adenoma was diagnosed based on a combination of increased GH levels, unsuppressed GH levels after a 75-g oral glucose tolerance test, increased insulin-like growth factor (IGF)-1 levels, and pathology studies in patients who underwent surgical treatment. A prolactin (PRL)-producing adenoma was diagnosed by a combination of increased prolactin levels, unchanging prolactin levels after a thyrotropin-releasing hormone test and GH-releasing peptide-2 test, or pathology studies in patients who underwent surgical treatment. An adrenocorticotropic hormone (ACTH)-producing adenoma was diagnosed based on a combination of increased levels of ACTH and cortisol in the morning, loss of diurnal ACTH and cortisol rhythm, high urinary levels of free cortisol, autonomic secretion of ACTH and cortisol confirmed by a 0.5 mg/8 mg dexamethasone suppression test, increased ACTH levels after a 1-desamino-8-D-arginine vasopressin test, and pathology studies in patients who underwent surgical treatment. A luteinizing hormone (LH)- or follicle stimulating hormone (FSH)-producing adenoma was diagnosed by a combination of increased LH or FSH levels, existing secondary hypergonadism, and pathology studies in patients who underwent surgical treatment. A thyroid-stimulating hormone (TSH)-producing adenoma was diagnosed by a combination of increased or normal TSH levels with mild hyperthyroidism, and pathology studies in patients who underwent surgical treatment.

2.5. Hormonal deficiency

The diagnosis of hormonal deficiency was performed in accordance with previous reports (20-23). In detail, GH deficiency was diagnosed by no or inadequate changes in GH levels after a GH-releasing peptide-2 test/insulin tolerance test/arginine test. ACTH deficiency was diagnosed by a combination of reduced ACTH levels and cortisol levels in the morning, and no or inadequate changes in ACTH levels or cortisol levels after a corticotropin-releasing hormone test. Deficiency in LH or FSH was diagnosed by a combination of reduced LH levels or FSH levels, no or inadequate changes in LH levels or FSH levels after a LH-releasing hormone test, and existing secondary hypogonadism. TSH deficiency was diagnosed by a combination of reduced TSH levels, no or inadequate changes in TSH levels after a thyrotropin-releasing hormone test, and existing secondary hypothyroidism. PRL deficiency was diagnosed by a combination of reduced PRL levels, no or inadequate changes in PRL levels after a thyrotropin-releasing hormone test. Central diabetes insipidus was diagnosed by a combination of increased urinary volume, low urinary osmolality and low ADH levels compared with serum osmolality, no or inadequate changes in ADH

levels after a 5% NaCl loading test/water restriction test, and increased ADH levels and decreased urinary volume after a 1-desamino-8-D-arginine vasopressin test.

2.6. Pituitary apoplexy

Pituitary apoplexy was diagnosed by the symptoms of sudden and severe headache and existing abrupt hemorrhage and/or infarction of the pituitary gland (24).

2.7. Statistical analyses

Data are the mean \pm standard deviation. Statistical analyses were performed using STATA[®] SE version 13.1 (Stata Corporation, College Station, TX, USA). Significance of differences between mean values was estimated by the Student's *t*-test. $P < 0.05$ was considered significant.

3. Results

Table 1 shows the clinical characteristics of the 65 patients who formed the study cohort. Their mean age was 55.6 ± 16.5 years; 34 patients (52.3%) were men and 31 (47.7%) were women. All patients underwent a detailed physical examination. 20 PIs (30.8%) were detected upon monitoring for headache, 10 (15.4%) at general check-up, 9 (13.8%) at monitoring for other diseases, and 8 (12.3%) at check-up for vertigo. In addition, 7 PIs (10.8%) were detected upon monitoring after trauma, 5 (7.7%) at check-up for hand paraesthesia, 3 (4.6%) upon monitoring for drowsiness, 1 (1.5%) at check-up for nausea, and 1 (1.5%) upon cancer staging (Table 2). The mean diameter of PIs was 22.2 ± 12.0 mm. Among the study cohort, 12 (18.5%) had diabetes mellitus, 32 (49.2%) had hypertension,

Table 1. Clinical characteristics of patients with pituitary incidentalomas

Items	<i>n</i> = 65
Age (years)	55.6 \pm 16.5
Sex (M/F)	34/31
Tumor diameter (mm)	22.2 \pm 12.0
Body mass index (kg/m ²)	23.0 \pm 3.5
Estimated glomerular filtration rate (mL/min/1.73 m ²)	80.1 \pm 18.3
Glycated hemoglobin (%)	6.01 \pm 1.23
Fasting plasma glucose (mg/dL)	101.0 \pm 25.2
Aspartate transaminase (U/L)	26.6 \pm 12.5
Alanine aminotransferase (U/L)	28.3 \pm 22.4
γ -glutamyl transferase (U/L)	32.3 \pm 25.9
Low-density lipoprotein-cholesterol (mg/dL)	123.0 \pm 34.4
High-density lipoprotein-cholesterol (mg/dL)	52.7 \pm 15.6
Triglyceride (mg/dL)	166.2 \pm 136.7
Systolic blood pressure (mmHg)	121.4 \pm 20.0
Diastolic blood pressure (mmHg)	74.8 \pm 14.0
Morbidity due to hypertension (%)	49.2
Morbidity due to diabetes mellitus (%)	18.5
Morbidity due to dyslipidemia (%)	69.2

Data are the mean \pm standard deviation.

and 45 (69.2%) had dyslipidemia.

The hormonal deficiency of these patients are shown in Table 3. 10 patients (15.4%) had a deficiency of ACTH, 16 (24.6%) had a deficiency of TSH, 21 (32.3%) had a deficiency of LH, 22 (33.8%) had a deficiency of FSH, 24 (36.9%) had a deficiency of GH, 2 (3.1%) had a deficiency of PRL, and 3 (4.6%) had central diabetes insipidus.

In regard to diagnosis, 33 patients (50.8%) had non-functional pituitary adenomas (NFPAs), 11 (16.9%) had Rathke's cleft cysts (RCCs), 7 (10.8%) had FPAs, 6 (9.2%) had benign extra-pituitary tumors (BEPTs), and 8 (12.3%) had malignant tumors (MTs). This information (along with the sub-classifications of FPAs, BEPTs, and MTs) is shown in Table 4.

We also investigated the clinical and endocrinological characteristics of respective tumor groups (Table 5). Patients with MTs were significantly younger (37.1 ± 16.1 vs. 60.1 ± 13.7 years, $p < 0.001$), had a significantly lower body mass index (19.5 ± 2.7 vs. 22.8 ± 2.9 , $p = 0.005$), as well as lower prevalence of hypertension (12.5% vs. 51.5%, $p = 0.047$) and dyslipidemia (37.5% vs. 72.7%, $p = 0.044$) than patients with NFPAs. Significantly more patients with MTs had central diabetes insipidus than patients with NFPAs (25.0% vs. 0.00%, $p = 0.011$). Patients with NFPAs had significantly greater prevalence of pituitary apoplexy (12.1%) than that of patients with FPAs (0%), BEPTs (0%), or MTs (0%) ($p = 0.044$ for all).

Table 2. Reasons for imaging examinations leading to detection of pituitary incidentalomas and the prevalence of pituitary apoplexy

Items	Number (%)
Headache	20 (30.8%)
General check-up	10 (15.4%)
Other diseases	9 (13.8%)
Vertigo	8 (12.3%)
After trauma	7 (10.8%)
Hand paraesthesia	5 (7.7%)
Drowsiness	3 (4.6%)
Nausea	1 (1.5%)
Cancer staging	1 (1.5%)
Pituitary apoplexy	5 (7.7%)

Table 3. Morbidity due to hormonal deficiency of patients with pituitary incidentalomas

Items	Number (%)
Deficiency of ACTH	10 (15.4%)
Deficiency of TSH	16 (24.6%)
Deficiency of LH	21 (32.3%)
Deficiency of FSH	22 (33.8%)
Deficiency of PRL	2 (3.1%)
Deficiency of GH	24 (36.9%)
Central diabetes insipidus	3 (4.6%)

ACTH, adrenocorticotropic hormone; FSH, follicle stimulating hormone; GH, growth hormone; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid stimulating hormone.

4. Discussion

Recent advances in imaging technology (especially those in magnetic resonance imaging) have resulted in an increase in PI detection, but few studies have focused on PIs (12-14). Freda and colleagues, in their guideline on the definition and recommendations for clinical management of PIs, emphasized the importance of thorough evaluation of PIs (1). In addition, tumors of the pituitary gland could lead to pituitary apoplexy. Thus, by undertaking highly detailed evaluations, we investigated the clinical and endocrinological characteristics of PIs, including the prevalence of pituitary apoplexy as well as the prevalence of hormonal disorders of respective tumor groups.

As the result of our investigations, the number of

NFPA was about half of all incidentalomas. Previously, it was reported that 77-81% patients with PIs were diagnosed as NFPA (13,14). The reason of disparity might be that all patients underwent highly detailed investigations in our study. Another reason might be that almost all cases of our study (except for 8 patients with RCCs and 1 patient with Prolactinoma) underwent a surgical procedure (including biopsy of the pituitary gland) and pathological investigations.

With respect to characteristics of respective tumor group, compared with patients with NFPA, patients with MTs were significantly younger and had a significantly lower body mass index, lower prevalence of hypertension, and lower prevalence of dyslipidemia. In addition, compared with patients with NFPA, significantly more individuals with MTs had central diabetes insipidus. On the other hand, with respect to tumor diameter, there was no significant difference between patients with NFPA or those with MTs, RCCs, FPA, or BEPTs. With regard to the function of the anterior pituitary gland, there were also no significant difference between patients with NFPA and patients with RCCs, FPA, BEPTs, or MTs. Considering MTs are commonly thought to increase in size rapidly, the reasons why there were no significant differences in both tumor diameter and the prevalence of anterior pituitary dysfunction between patients with NFPA and those with MTs are not entirely clear, but may reflect the difficulty of making the diagnosis without undertaking a detailed physical examination or pathology studies. Conversely, the prevalence of pituitary apoplexy in patients with NFPA was significantly higher than that of patients with FPA, BEPTs, or MTs. McCabe and colleagues reported an increase of mRNA expression

Table 4. Diagnosis of patients with pituitary incidentalomas

Items	Number (%)
Non-functional pituitary adenoma	33 (50.8%)
Rathke's cleft cyst	11 (16.9%)
Functional pituitary adenoma	7 (10.8%)
GH-producing adenoma	2 (3.1%)
PRL-producing adenoma	4 (6.2%)
FSH-producing adenoma	1 (1.5%)
Benign extra-pituitary tumor	6 (9.2%)
Meningioma	3 (4.6%)
Craniopharyngioma	3 (4.6%)
Malignant tumor	8 (12.3%)
Astrocytoma	1 (1.5%)
Glioma	1 (1.5%)
Glioblastoma	1 (1.5%)
Germinoma (unclassifiable)	2 (3.1%)
Malignant lymphoma	2 (3.1%)
Metastasis of squamous cell carcinoma of the lung	1 (1.5%)

Table 5. Clinical characteristics of patients with pituitary incidentalomas

Items	Non-functional pituitary adenoma	Rathke's cleft cyst	Functional pituitary adenoma	Benign extra-pituitary tumor	Malignant tumor
Number	33	11	7	6	8
Age (years)	60.1 ± 13.7*	52.4 ± 15.7	58.7 ± 16.7	54.3 ± 19.4	37.1 ± 16.1*
Male (%)	48.5	54.5	71.4	33.3	62.5
Tumor diameter (mm)	21.4 ± 4.9	16.4 ± 8.9	32.0 ± 28.9	26.5 ± 10.0	23.5 ± 11.1
Body mass index (kg/m ²)	22.8 ± 2.9 [§]	24.4 ± 4.2	24.4 ± 2.0	24.4 ± 3.6	19.5 ± 2.7 [§]
Hypertension (%)	51.5 [#]	45.4	71.4	66.7	12.5 [#]
Diabetes mellitus (%)	18.2	18.2	28.6	16.7	12.5
Dyslipidemia (%)	72.7 ^{&}	81.8	85.7	50.0	37.5 ^{&}
Deficiency of ACTH (%)	18.2	18.2	14.3	16.7	50.0
Deficiency of TSH (%)	24.2	18.2	14.3	16.7	50.0
Deficiency of LH (%)	33.3	27.3	28.6	16.7	50.0
Deficiency of FSH (%)	33.3	27.3	28.6	33.3	50.0
Deficiency of PRL (%)	3.0	9.0	0	0	0
Deficiency of GH (%)	36.4	36.4	28.6	16.7	62.5
Central diabetes insipidus (%)	0 [†]	0	0	16.7	25.0 [†]
Pituitary apoplexy (%)	12.1 ^{‡§}	9.0	0 [‡]	0 [‡]	0 [‡]

Patients with malignant tumors (MTs) were significantly younger and had significantly lower body mass index, less hypertension, and less dyslipidemia than those with non-functional pituitary adenomas (NFPA) (*§#&). Patients with MTs had significantly more central diabetes insipidus than those with NFPA (*). Patients with NFPA had significantly more pituitary apoplexy than those with functional pituitary adenomas (FPA), benign extra-pituitary tumors (BEPTs), and MTs (‡§). The significance of differences between means was estimated by the Student's *t*-test.

of vascular endothelial growth factor in patients with NFPAs compared with that in patients with other types of pituitary-gland tumors and healthy controls (25), which could support our results regarding the prevalence of pituitary apoplexy. In addition, we found no significant difference in the prevalence of pituitary apoplexy between patients with NFPAs or RCCs. Some scholars have reported that pituitary apoplexy can occur in patients with RCCs (26-28). Indeed, Hama and co-workers reported inflammation in the epithelium of RCCs (29), which could support the prevalence of pituitary apoplexy observed in patients with RCCs in the present study. This finding has not been reported adequately.

This study had one limitation. Our study cohort was small because PIs are relatively rare which caused difficulty in our analysis. Future studies with much larger study cohorts are needed to confirm our results.

In conclusion, our study provided insights into the clinical and endocrinological characteristics of PIs. PIs should undergo highly detailed clinical and endocrinological investigations. In addition, our study also indicated that young and lean patients with central diabetes insipidus might warrant particularly careful investigation considering MTs.

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