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Clinical evaluations of pituitary apoplexy in incidental nonfunctional pituitary adenomas

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Abstract

Pituitary apoplexy is an uncommon syndrome that often results in spontaneous hemorrhage or infarction of pituitary tumors or glands. We previously reported pituitary apoplexy occurred most frequently in nonfunctional pituitary adenomas among all types of pituitary incidentalomas. In the present study, we aimed to investigate the characteristics of pituitary apoplexy in patients with incidental nonfunctional pituitary adenomas. 65 patients with pituitary incidentaloma were enrolled. All patients underwent clinical/endocrinological/pathological investigations. As a result, 33 patients were diagnosed with nonfunctional pituitary adenomas. Of these, 12.1% of patients had pituitary apoplexy. There was no difference in tumor diameter, age, or sex between the apoplexy and the non-apoplexy groups. However, the liver enzymes aspartate transaminase and alanine aminotransferase were significantly higher, and plasma sodium and chloride levels were significantly lower in the apoplexy group than in the non-apoplexy group (each $P < .05$). In addition, low-density lipoprotein-cholesterol was significantly higher in the apoplexy group than in the non-apoplexy group ($P < .05$). Besides, thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, and prolactin deficiencies were significantly more frequent in the apoplexy group than in the non-apoplexy group (each $P < .05$), and growth hormone and adrenocorticotropic hormone deficiencies were more frequent in the apoplexy group than in the non-apoplexy group ($P = .09$ and.08, respectively). Furthermore, tumor diameter was not associated with pituitary apoplexy, whereas thyroid-stimulating hormone, luteinizing hormone, and follicle-stimulating hormone deficiencies were significantly associated with the apoplexy group (each $P < .05$). Hence, the present study indicated that pituitary apoplexy could not be related to tumor diameter. Moreover, hormonal deficiencies, hepatic dysfunction, hyponatremia or hypochloremia, and dyslipidemia might be indicators of pituitary apoplexy. There could be the possibility the treatment for dyslipidemia prevents pituitary apoplexy.

Abbreviations: ACTH = adrenocorticotropic hormone, ADH = antidiuretic hormone, ALT = alanine aminotransferase, AST = aspartate transaminase, FSH = follicle-stimulating hormone, GH = growth hormone, LDL = low-density lipoprotein, LH = luteinizing hormone, PRL = prolactin, TSH = thyroid-stimulating hormone.

Keywords: hormonal deficiency, nonfunctional pituitary adenoma, pituitary apoplexy, pituitary incidentaloma

1. Introduction

Pituitary apoplexy is a life-threatening syndrome attributed to hemorrhage or hemorrhagic infarction of pituitary tumors or pituitary glands.[1,2] In the earliest reports, patients with pituitary tumors presenting with sudden onset of headache, vomiting, visual impairment, diplopia, disturbances of consciousness, and hormonal dysfunction had pituitary apoplexy.[1,3] According to a previous report, the incidence of apoplexy among pituitary adenomas is 2% to 12%.[4] Hence, pituitary apoplexy could be a rare syndrome, and few series have examined it in the literature. Recently, we demonstrated that nonfunctioning pituitary adenomas could most frequently complicate pituitary apoplexy among all types of pituitary incidentalomas (i.e., functioning pituitary tumors and malignant tumors).[5] Another study also demonstrated that more than 70% of adenomas with apoplexy were nonfunctioning pituitary adenomas.[6] McCabe et al[7] also reported that nonfunctioning pituitary adenomas with higher expression of vascular endothelial growth factor and its receptors led to

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pituitary apoplexy than other types of pituitary gland tumors and healthy controls. However, detailed clinical investigations have not yet been adequately performed. Here, we demonstrated pituitary apoplexy's clinical, endocrinological, and pathological characteristics among incidentally discovered nonfunctional pituitary adenomas.

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 all patients for participation in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Study participants

The study cohort is shown in Figure 1. In the present study, 65 patients with pituitary incidentaloma were enrolled at Chikushi Hospital within Fukuoka University or Yamagata University Hospital from April 2015 to March 2018. Among them, 33 individuals were found to have incidental nonfunctional pituitary adenomas. Pituitary incidentalomas were diagnosed according to the following criteria: incidental detection on imaging examinations undertaken for monitoring non-endocrine diseases; general health status; various symptoms (such as headache and vertigo) not considered to be associated with the lesion, defined by the Endocrine Society guidelines.[8] In addition, all study participants underwent endocrinological evaluations, laboratory tests, surgery, and pathological investigations, which revealed nonfunctional pituitary adenomas, as previously described.[5]

Pituitary apoplexy was diagnosed by the symptoms of sudden and severe headache and existing abrupt hemorrhage and/or infarction of the pituitary gland.[4,5]

2.3. Methods and disease definitions

We collected data on age, sex, tumor diameter, medical history, physical examination, laboratory tests, endocrinological evaluations, and pathological findings for all patients (including patients with pituitary apoplexy). We then investigated the differences and relationships between the apoplexy and the non-apoplexy groups for any parameter.

Hypertension was defined as any combination of systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or the use of antihypertensive drugs. Diabetes mellitus was defined as any combination of fasting plasma glucose ≥ 126 mg/dL, random plasma glucose ≥ 200 mg/dL, glycated hemoglobin ≥ 6.5%, or the use of antidiabetic agents. Dyslipidemia was defined as any combination of total cholesterol ≥ 220 mg/dL, low-density lipoprotein (LDL) cholesterol ≥ 140 mg/dL, high-density lipoprotein cholesterol < 40 mg/dL, triglyceride ≥ 150 mg/dL, or the use of lipid-lowering drugs. Liver dysfunction was defined as any combination of aspartate transaminase (AST) ≥ 30 U/L; alanine aminotransferase (ALT) ≥ 30 U/L; and γ-glutamyl transferase (γ-glutamyl transferase) ≥ 35 U/L. Regarding hormonal deficiencies, the diagnosis of anterior adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), growth hormone (GH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin (PRL) and posterior pituitary hormonal deficiencies (central diabetes insipidus) was performed as previously described.[5] In detail, 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. TSH deficiency was diagnosed

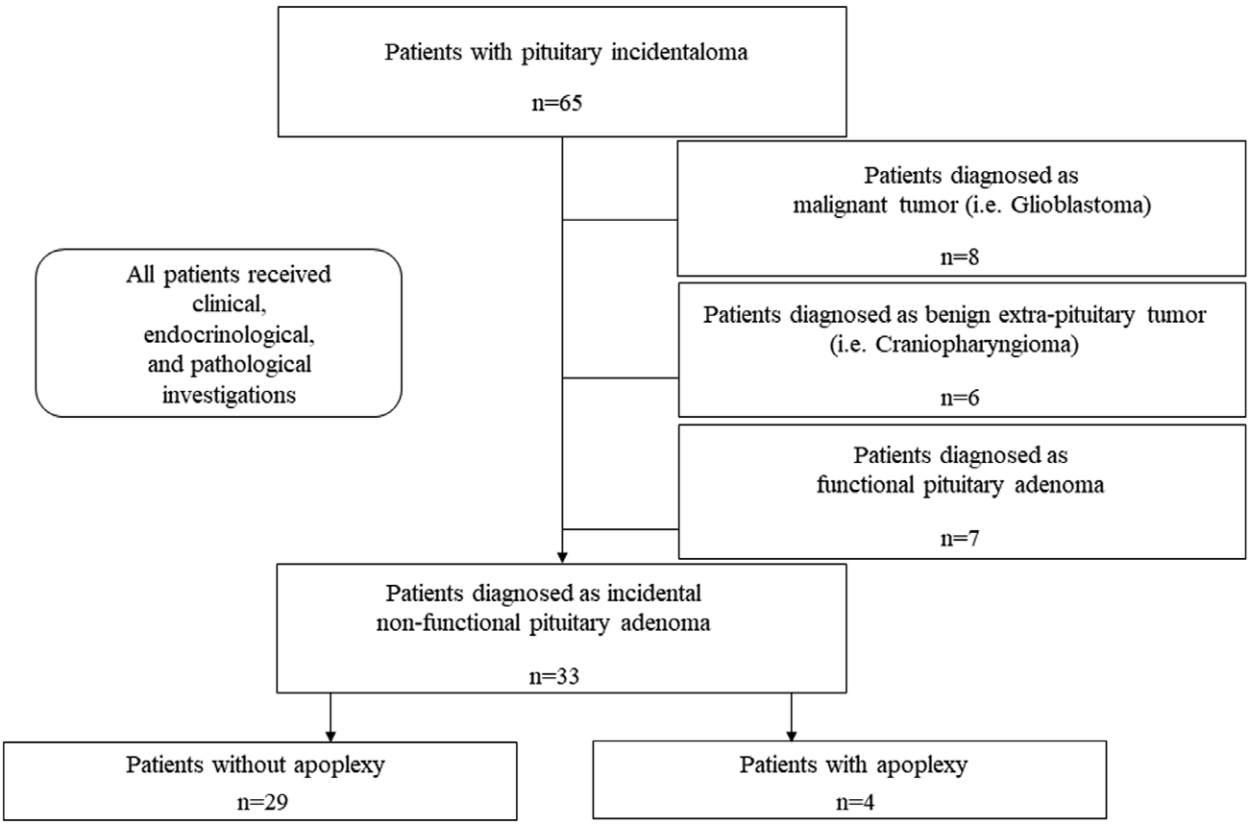

Figure 1. Cohort diagram of this study.

by a combination of reduced TSH levels, no or inadequate changes in TSH levels after a thyrotropin-releasing hormone test, and existing secondary hypothyroidism. GH deficiency was diagnosed by no or inadequate changes in GH levels after a GH-releasing peptide-2 test/insulin tolerance test/arginine 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. 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 antidiuretic hormone (ADH) levels compared with serum osmolality, no or inadequate changes in ADH levels after a water restriction test/5% NaCl loading test, and increased ADH levels and decreased urinary volume after a 1-desamino-8-D-arginine vasopressin administration.

2.4. Statistical analysis

Data are shown as the mean ± standard deviation. Statistical analyses were performed using the Stata SE version 16 (StataCorp. 2019. Stata statistical software: Release 16, Stata Corp LLC, College Station, TX). The Student's *t* test was used to estimate the significance of differences between mean values. The relationship was examined using the Fisher's exact test. Statistical significance was set at $P < .05$.

3. Results

Table 1 shows the clinical characteristics of patients in the study cohort. In this study, 4 (12.1%) of 33 patients with nonfunctional pituitary incidentalomas had pituitary involvement. The Student's *t* test showed that there was no difference in tumor diameter, age, or sex between the apoplexy and non-apoplexy groups; however, the liver enzymes AST and ALT were significantly higher, and plasma sodium and chloride levels were significantly lower in the apoplexy group than in the non-apoplexy group ($P < .05$). In addition, LDL-cholesterol levels were significantly higher in the apoplexy group than in the non-apoplexy group ($P = .02$). There was no difference in the prevalence of dyslipidemia between the apoplexy and non-apoplexy groups. However, the number of patients who were medicated for dyslipidemia was significantly higher in the apoplexy group than in the non-apoplexy group ($P < .01$; 41.3% vs 0%) (Table 1). Meanwhile, TSH, LH, FSH, and PRL deficiencies were significantly more frequent in the apoplexy group (each $P < .05$). There were no patients in the non-apoplexy group that had PRL deficiencies. GH and ACTH deficiencies were suggested to be more frequent in the apoplexy group, but not significantly ($P = .09$ and .08, respectively) (Table 2). In addition, the Fisher's test showed that the tumor diameter was not associated with pituitary apoplexy. Regarding hormonal deficiencies, TSH, LH, and FSH deficiencies were significantly associated with pituitary apoplexy (each $P < .05$), while ACTH, GH, and PRL deficiencies were not associated with pituitary apoplexy (Table 3).

4. Discussion

There is a slight overall male to female (1.6:1.0) preponderance in the literature. The youngest reported patient was 6 years of age, whereas the oldest was 90, with a mean age of 50.9 years and a median age of 52 years. In this report, the prevalence of ACTH deficiency was 40% to 100%, TSH deficiency was 25% to 80%, and LH/FSH deficiency was 60% to 100%.[6] Veldhuis and Hammond also demonstrated that 88% of patients had GH deficiency, 76% had LH/FSH deficiency, 66% had ACTH deficiency, and 2% to 3% had diabetes insipidus in a pituitary apoplexy cohort.[9] Our study investigated patients with nonfunctioning pituitary adenomas, which were reported to cause pituitary apoplexy most frequently. Student's *t* test showed that TSH, LH, FSH, and PRL deficiency rates were significantly higher in the apoplexy group, and GH, ACTH, and PRL deficiencies were more frequent, but not significantly, in the apoplexy group. The objectives of our study were generally similar

Table 1

Clinical characteristics of patients and comparison with or without apoplexy.

	All patients (n = 33)	Without apoplexy (n = 29)	With apoplexy (n = 4)	*P*
Age (yr)	60.1 ± 13.7	59.8 ± 13.78	62.3 ± 14.5	.75
Gender (Female/male)	16/17	14/15	2/2	.95
Maximum tumor size (mm)	21.4 ± 4.9	21.6 ± 5.1	19.3 ± 2.9	.36
BMI (kg/m^2)	22.8 ± 2.9	22.8 ± 3.0	22.8 ± 2.3	.96
Systolic Blood Pressure (mm Hg)	121.2 ± 17.6	122.5 ± 18.3	111.8 ± 7.4	.26
Diastolic blood pressure (mm Hg)	73.4 ± 12.2	73.9 ± 12.9	69.5 ± 5.6	.51
HbA1c (%)	5.8 ± 0.5	5.8 ± 0.5	6.1 ± 0.6	.32
eGFR (mL/min/1.73 m^2)	75.6 ± 16.6	75.2 ± 15.8	78.2 ± 24.6	.74
AST (U/L)	24.5 ± 6.8	23.0 ± 5.6	35.3 ± 5.1	<.01*
ALT (U/L)	23.4 ± 14.4	20.6 ± 9.0	43.5 ± 29.1	<.01*
γ-GTP (U/L)	28.0 ± 22.0	28.1 ± 22.8	27.3 ± 17.9	.94
LDL-cholesterol (mg/dL)	123.1 ± 31.2	118.6 ± 28.8	155.5 ± 31.4	.02*
HDL-cholesterol (mg/dL)	55.1 ± 16.7	55.9 ± 17.4	49.0 ± 9.6	.44
Triglyceride (mg/dL)	188.8 ± 176.5	181.4 ± 182.5	242.8 ± 129.5	.53
Na (mmol/L)	140.1 ± 2.5	140.4 ± 1.9	137.3 ± 4.8	.01*
K (mmol/L)	4.0 ± 0.4	4.0 ± 0.4	4.4 ± 0.5	.12
Cl (mmol/L)	105.1 ± 2.9	105.8 ± 1.8	100.0 ± 4.0	<.01*
Hypertension (%)	51.5	51.7	50.0	.95
Diabetes mellitus (%)	18.2	17.2	25.0	.71
Dyslipidemia (%)	72.7	72.4	75.0	.92
Medication for hypertension (%)	39.4	37.9	50.0	.66
Medication for diabetes mellitus (%)	9.1	10.3	0.0	.08
Medication for dyslipidemia (%)	36.4	41.3	0.0	<.01*

Data are shown as mean ± standard deviation.

ALT = alanine aminotransferase, AST = aspartate transaminase, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, LDL = low-density lipoprotein, γ-GTP = γ-glutamyl transferase.

*Statistical significance was set at $P < .05$.

Table 2

Hormonal deficiencies of patients and comparison with or without apoplexy.

	All patients (n = 33)	Without apoplexy (n = 29)	With apoplexy (n = 4)	*P*
Deficiency of ACTH (%)	18.2	13.8	50.0	.08
Deficiency of TSH (%)	24.2	17.2	75.0	.01*
Deficiency of GH (%)	36.4	31.0	75.0	.09
Deficiency of LH (%)	33.3	24.1	100.0	<.01*
Deficiency of FSH (%)	33.3	24.1	100.0	<.01*
Deficiency of PRL (%)	3.0	0.0	25.0	<.01*
Central diabetes insipidus (%)	0.0	0.0	0.0	N.A.

ACTH = adrenocorticotropic hormone, FSH = follicle-stimulating hormone, GH = growth hormone, LH = luteinizing hormone, N.A. = not assessed, PRL = prolactin, TSH = thyroid-stimulating hormone.
*Statistical significance was set at $P < .05$.

Table 3

Relationship between pituitary apoplexy and tumor diameter/hormonal deficiencies examined with the Fisher's exact test.

	Without apoplexy (n = 29)	With apoplexy (n = 4)	*P*
Tumor diameter (mm)			
Over 20 (or = 20)	17	2	1.00
Less than 20	12	2	
ACTH deficiency			
Presence	4	2	.14
Absence	25	2	
TSH deficiency			
Presence	5	3	.04*
Absence	24	1	
GH deficiency			
Presence	9	3	.13
Absence	20	1	
LH deficiency			
Presence	8	4	.01*
Absence	21	0	
FSH deficiency			
Presence	8	4	.01*
Absence	21	0	
PRL deficiency			
Presence	29	3	.12
Absence	0	1	

ACTH = adrenocorticotropic hormone, FSH = follicle-stimulating hormone, GH = growth hormone, LH = luteinizing hormone, PRL = prolactin, TSH = thyroid-stimulating hormone.
*Statistical significance was set at $P < .05$.

in age and sex compared to previous reports. There were no significant differences in tumor diameter between the apoplexy and non-apoplexy groups. The results of our study differed from those of previous reports regarding hormonal deficiencies and the effect of tumor diameter. Therefore, we performed Fisher's exact test to confirm these results. Fisher's exact test showed that TSH, LH, and FSH deficiencies were significantly associated with pituitary apoplexy, while deficiencies in other hormones and tumor diameter were not associated with pituitary apoplexy. Regarding hormonal deficiencies, the cause of the difference could have been because our study cohort was small. In addition, regarding PRL deficiency, there was a significant difference between the apoplexy and non-apoplexy groups using Student's *t* test, although there was no relationship between PRL deficiency and pituitary apoplexy according to Fisher's exact test. Regarding patients with pituitary apoplexy, those with normal or elevated serum prolactin levels at presentation had less severe hypopituitarism and recovered pituitary function after surgery than those with low serum prolactin levels.[10] Considering that PRL deficiency was not observed in the non-apoplexy group in our study, the decrease in PRL secretion may be a predictor of pituitary apoplexy.

Our study results indicated that tumor diameter was not associated with pituitary apoplexy. There have been previous reports of pituitary apoplexy even in pituitary microadenomas (<10 mm).[11,12] While pituitary apoplexy has been generally considered to occur in macroadenomas, our study and previous reports show that pituitary apoplexy was not related to tumor diameter. Therefore, clinicians should consider the possibility of apoplexy even in microadenomas.

In contrast, the plasma sodium and chloride levels were significantly lower in the apoplexy group. It has been known that adrenal insufficiency could cause hyponatremia. One of the possible mechanisms could be mineralocorticoid deficiency, which was observed in primary/secondary/hypothalamic adrenal insufficiency. Moreover, hyponatremia can be caused by an inappropriate increase in vasopressin secretion/action due to cortisol deficiency.[13] Hypothyroidism can also cause hyponatremia through a similar mechanism of action.[13] ACTH and TSH deficiencies might have contributed to electrolyte imbalance in the apoplexy group.

Our study also showed that liver enzymes AST and ALT were significantly higher in the apoplexy group than in the non-apoplexy group. All patients with hepatic dysfunction in the apoplexy group had GH deficiency. Patients with GH deficiency have an increased prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis.[14] In our study, hepatic dysfunction was not solely caused by GH deficiency. A previous report indicated that pituitary apoplexy could cause an increase in inflammatory cytokines.[2] Furthermore, inflammatory cytokines are reported to cause liver dysfunction.[15,16] Actually, the C-reactive protein of patients with pituitary apoplexy were

raised (mean value: 4.05 mg/dL). Hence, liver dysfunction in the apoplexy group could be caused by inflammation of the pituitary and increased levels of inflammatory cytokines, in addition to the effect of GH deficiency.

The relationship between dyslipidemia and pituitary apoplexy has not been previously reported. In this study:

1. There were no differences in morbidity of dyslipidemia between the apoplexy group and the non-apoplexy group.
2. The levels of LDL-cholesterol in the patients with apoplexy were significantly higher than in those without apoplexy.
3. There were significantly fewer patients with medication for dyslipidemia in the apoplexy group than in the non-apoplexy group (No patients were medicated in the apoplexy group and 41.3% of patients were medicated).

The pathophysiology of pituitary apoplexy is known to be hemorrhage or hemorrhagic infarction of pituitary tumors or pituitary glands Pituitary apoplexy could associate with micro/macrovascular diseases, partly caused by dyslipidemia. In this study, at least 3 of 4 patients with pituitary apoplexy in this study had dyslipidemia before pituitary apoplexy (The lipid profiles of 1 patient had not been checked before pituitary apoplexy occurred). Hence, treatment for dyslipidemia could have the efficacy of preventing pituitary apoplexy. In addition, TSH/LH/FSH/GH deficiencies have been well-known to cause dyslipidemia. 3 of 4 patients with pituitary apoplexy had TSH/GH deficiencies and all patients with pituitary apoplexy had LH/FSH deficiencies. Thus, the replacement treatment of these hormone deficiencies could improve their lipid profile.

5. Conclusion

Our study provides insight into pituitary apoplexy's clinical and endocrinological characteristics. Pituitary apoplexy is generally considered to occur in macroadenomas; however, this study suggests that it is not related to tumor diameter and that it is necessary to consider the possibility of apoplexy without regard for tumor diameters. In addition, if patients have hormonal deficiencies, hepatic dysfunction, hyponatremia or hypochloremia, and dyslipidemia, clinicians should consider pituitary apoplexy. The treatment of dyslipidemia might prevent pituitary apoplexy. Our study cohort was small because pituitary apoplexy is a rare syndrome and the objectives were limited to incidental nonfunctional pituitary adenomas. Hence, future studies are required to confirm our results.

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