Natural course of incidentally found nonfunctioning pituitary adenoma, with special reference to pituitary apoplexy during follow-up examination

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Object. The increase in the incidental detection of asymptomatic pituitary adenomas, known as “pituitary incidentalomas,” led the authors to conduct a survey of the natural course of these lesions.

Methods. Forty-two patients with clinically nonfunctioning pituitary adenomas who had manifested no neurological or endocrinological disorders were monitored with magnetic resonance imaging studies. The follow-up period ranged from 10.8 to 168.2 months (mean ± standard deviation, 61.9 ± 38.2 months). The mean initial tumor size was 18.3 ± 7 mm.

In 21 patients, the tumor increased by at least 10% of its measured size on detection. This increase was first detected between 8.4 and 58.8 months (mean 31.8 ± 17.6 months) after diagnosis. There was no correlation between the original tumor size, patient age, or the presence of intratumoral cysts and tumor growth. Symptoms were noted in 10 patients during follow up; in four, extensive tumor necrosis accompanied hemorrhage, leading to severe headache, acute ophthalmological symptoms, and panhypopituitarism, which was indicative of pituitary apoplexy. Transsphe- 

coidal surgery was performed in 12 patients with enlarged tumors, including three with apoplexy. With the exception of one apoplectic patient, visual function was recovered in all who underwent surgery. All apoplectic patients continue to manifest hypopituitarism.

Conclusions. In the course of 4 years, the size of the incidentalomas increased in 40% of 42 patients and became symptomatic in 20%. During the 5-year follow up, pituitary apoplexy developed in 9.5%. These findings may justify early intervention, especially in young individuals with incidentally found macroadenoma.

KEY WORDS • pituitary adenoma • incidentaloma • pituitary apoplexy

Abbreviations used in this paper: LHRH = luteinizing hormone–releasing hormone; MR = magnetic resonance; TSS = transsphe- 

coidal surgery.

The ready availability of MR imaging has led to an increase in the detection of asymptomatic pituitary adenomas, known as “pituitary incidentalomas.” Strategies for managing these lesions have yet to be developed. Pituitary adenomas are slow-growing neoplasms; symptoms are reversible if the tumors are removed soon after any signs emerge. Although most pituitary incidentalomas can be safely monitored until early signs appear, pituitary apoplexy as a result of acute intratumoral hemorrhage is sometimes irreversible despite emergency surgery. In our efforts to develop a strategy for the management of pituitary incidentalomas, we examined their natural course and the incidence of pituitary apoplexy.

Clinical Material and Methods

Patient Population

Between January 1990 and December 2002, 139 patients with a pituitary mass lesion but no overt symptoms were referred to Hiroshima University Hospital. All underwent diagnostic MR imaging examinations. We excluded from this study 73 patients with thin-walled cystic lesions strongly indicative of Rathke cleft cyst. The lesions in the remaining 66 patients consisted of a solid portion that was less intensely enhanced on imaging than the pituitary gland, which was pushed against the lesion periphery or displaced laterally or superiorly by the tumor. These MR imaging characteristics led to a diagnosis of pituitary adenoma.

Ten patients were omitted from the cohort because they manifested insidious symptoms: three demonstrated visual field deficits on static perimetry examination, and seven demonstrated panhypopituitarism (three patients) or hormonal hypersecretion (for example, hypersomatotropinemia or hyperprolactinemia; four patients) on endocrinological examination. Another 14 patients were excluded at their own request or because they had undergone TSS for chiasmal compression within 6 months of the pituitary adenoma diagnosis.

The remaining 42 patients with clinically nonfunctioning pituitary adenoma were scheduled for regular follow-up
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examinations. These patients consisted of 18 men and 24 women, ranging in age from 34 to 83 years (mean ± standard deviation, 61 ± 10.4; Table 1). The tumors were classified as microadenomas (< 10 mm) in five patients and as macroadenomas (≥ 10 mm) in 37; 30 lesions demonstrated suprasellar extension on initial MR images. The maximal diameter of 37 tumors was the lesion’s height; it was the tumor’s width in five lesions. The tumor heights ranged from 7 to 42 mm (mean 18 ± 7 mm).

The factors that led to the initial screening with MR imaging in the 42 patients were chronic headache in 13 patients, brain checkup in nine, head injury and dizziness in five each, cerebrovascular disease in four, and visual disturbance irrelevant to the adenoma in two. One patient each was screened because of facial nerve palsy, seizure, cold intolerance, and another brain tumor.

Conducted Studies

All 42 patients underwent initial ophthalmological examination including dynamic and static perimetry. Within 3 months of the initial visit, all patients underwent a triple-bolus injection test (0.1 U/kg regular insulin, 500 μg thyrotropin-releasing hormone, and 100 μg LHRH to assess hypothalamopituitary function. None of the patients manifested visual dysfunction or severely impaired pituitary function requiring cortisol and/or thyroxine replacement therapy.

The patients were scheduled to undergo MR imaging 6 and 12 months after the initial diagnosis and once a year thereafter. The follow-up period ranged from 10.8 to 168.2 months of the initial visit, all patients underwent a triple-bolus injection test (0.1 U/kg regular insulin, 500 μg thyrotropin-releasing hormone, and 100 μg LHRH to assess hypothalamopituitary function. None of the patients manifested visual dysfunction or severely impaired pituitary function requiring cortisol and/or thyroxine replacement therapy.

The patients were scheduled to undergo MR imaging 6 and 12 months after the initial diagnosis and once a year thereafter. The follow-up period ranged from 10.8 to 168.2 months (mean 61.9 ± 38.2 months). Tumor enlargement was recorded when the lesion’s height surpassed 110% of its initial measured height. During the follow-up studies, on detection of either significant compression of the optic chiasm or minute visual field defects at the perimeter, TSS was recommended.

Results

Changes in Tumor Size

During the course of 61.9 months, the tumor size increased in 21 of 42 patients (Fig. 1), decreased in one, and remained unchanged in 20. Increases were first detected at 8.4 to 58.8 months after diagnosis (Fig. 2) and ranged from 10 to 82% (Fig. 3). There was no correlation between a patient’s age on tumor detection, sex, the tumor type (micro-or macroadenoma) or size, or the presence of intratumoral cysts and the likelihood of tumor enlargement (Mann–Whitney U-test; Table 1).

Of the 21 patients with tumor enlargement, 10 manifested symptoms including visual field defects, double vision, and panhypopituitarism (Fig. 4); four exhibited pituitary apoplexy. The initial height of the 10 symptomatic tumors ranged from 17 to 24 mm (mean 19.7 ± 2 mm). The risk for symptomatic tumor enlargement was significantly greater in lesions whose height on detection exceeded 15 mm (28 lesions) than in those smaller than 15 mm (14 lesions; Cox–Mantel test, p = 0.007). Transsphenoidal surgery was performed in nine of the 10 symptomatic patients and in three with asymptomatic enlargement.

Pituitary Apoplexy

Pituitary apoplexy developed in four patients during the follow up; they presented with severe headache, visual symptoms, and/or acute onset of hypopituitarism. Magnetic resonance imaging results showed hemorrhagic infarction of the tumor; surrounding tissues manifested the characteristic appearance (Figs. 5–8). Among the four patients with apoplexy, the initial tumor size was 18 and 24 mm in one patient each and 20 mm in two patients. These patients experienced apoplexy 20, 24, 26, and 56 months after a diagnosis had been made. An endocrinological diagnosis of panhypopituitarism was made in each of these patients; monoclonal parathyroid hyperplasia and acute deterioration of visual acuity developed in two patients each. In a 74-year-old man, a possible precipitating factor for the apoplexy was the injection of an LHRH analog for the treatment of prostate cancer. Of these four patients, three underwent TSS. Visual disturbance persisted in one patient. All four patients continue to receive regular cortisol and thyroxine replacement.

Surgical Results

In addition to the three patients with apoplexy, six with symptomatic and three with asymptomatic tumor enlargement underwent TSS with successful gross-total tumor removal. At 6 months postsurgery, the visual field was normal in all symptomatic patients. None of the patients who had undergone surgery manifested postoperative hypopituitarism requiring cortisol and/or thyroxine replacement therapy.

Discussion

In autopsy series, the incidence of pituitary microadenoma (lesion size < 10 mm) and macroadenoma (lesion size ≥ 10 mm) has ranged from 1.5 to 26.7% and 0 to

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* NA = not applicable.
† Values are presented as the means ± standard deviations.

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Fig. 1. Images obtained in a 46-year-old man with chronic headache. Coronal (a) and sagittal (b) MR images demonstrating an asymptomatic pituitary adenoma with a height of 17 mm. Perimetry maps showing normal visual fields in both the left (c) and right (d) eyes. Follow-up MR images obtained 28 months postdiagnosis showed an increase in tumor height to 22 mm. Coronal (e) and sagittal (f) MR images obtained 71 months postdiagnosis revealing a tumor height of 25 mm. Perimetry maps demonstrating the appearance of visual field defects in the left (g) and right (h) eyes.

Fig. 2. Kaplan–Meier survival curve demonstrating tumor enlargement–free survival in 42 patients with incidentally found pituitary adenoma.

Fig. 3. Graph showing the percentage changes in the height of 21 enlarged adenomas. The tumor height measured at the latest follow-up examination was 110 to 180% of the height measured on initial diagnosis.
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1.3%, respectively.\textsuperscript{15,21,24} Unenhanced MR images not targeted on the pituitary region have revealed macroadenomas in six (0.16%) of 3672 healthy volunteers and no microadenomas.\textsuperscript{33} At our affiliated hospitals, macroadenomas were found in five (0.11%) of 4370 healthy volunteers who had undergone brain examinations with axial T\textsubscript{1} - and T\textsubscript{2}-weighted MR imaging (unpublished data). In contrast, enhanced MR imaging studies targeting the pituitary region demonstrated microlesions in 10% of healthy volunteers.\textsuperscript{10}

Given that the optimal strategy for managing incidentally found pituitary adenomas remains to be established, we attempted to elucidate the natural course of these tumors. In the current study we included only patients with clinically nonfunctioning adenomas. Because surgical removal remains the treatment of choice, the timing of the operation is the main issue in the management of these adenomas. Although prolactinomas are usually controlled with dopamine agonists alone, preclinical adrenocorticotropic hormone– or growth hormone–producing adenomas require early surgical intervention.\textsuperscript{1,14} At the time of initial diagnosis, all patients in our study underwent static and dynamic perimetry as well as anterior pituitary provocation tests. We excluded

\begin{figure}[h]
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\caption{Kaplan–Meier survival curve demonstrating symptom-free survival in patients with incidentally found pituitary adenomas. The solid line represents all 42 patients. Open circles indicate cases with pituitary apoplexy. The thin dotted line indicates 28 patients with adenomas whose initial size was larger than 15 mm, whereas the bold dotted and dashed line represents 14 patients with adenomas whose initial size was 15 mm or smaller. The risk for symptomatic tumor enlargement was significantly greater with tumors whose height on detection exceeded 15 mm compared with those whose height was less than 15 mm (Cox–Mantel test, p = 0.007).}
\end{figure}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{image2.png}
\caption{Coronal (a) and sagittal (b) MR images obtained in a 52-year old man, revealing a pituitary adenoma with slight suprasellar extension. Coronal (c) and sagittal (d) follow-up MR images obtained 16 months postdiagnosis and 2 days after his apoplectic attack, showing hemorrhagic infarction in the tumor and parasellar dural enhancement. These findings are compatible with pituitary apoplexy. This case was previously reported in Arita, et al., 2001.}
\end{figure}
patients with subtle visual field defects and secondary hypoadrenocorticism and/or hypothyroidism; therefore, all 42 tumors were confirmed to be clinically nonfunctioning, purely asymptomatic pituitary adenomas.

Authors of a Japanese survey of pituitary incidentalomas found that 23 (20%) of 115 solid sellar tumors thought to be nonfunctioning pituitary adenomas increased in size during a mean observation period of 26.9 months. Donovan and Corenblum, who prospectively monitored 31 pituitary incidentalomas, found in the macroadenoma subset that the size of five (31.3%) of 16 tumors increased during a mean follow-up period of 6.1 years. Reincke, et al., followed up 14 patients for a mean of 22 months; three patients (21.4%) demonstrated enlargement of their pituitary incidentalomas. Feldkamp, et al., observed tumor enlargement in 3.2% of 31 patients with microadenomas and in 26.3% of 19 patients with macroadenomas during 2.7 years of follow up.

In the present series, 40% of the patients manifested tumor enlargement within 4 years after an initial diagnosis (Fig. 2). This rate is higher than that reported previously, possibly due to our patient selection criteria. From an original sample of 139 patients, we excluded 73 (52.5%) with suspected Rathke cleft cysts, which rarely grow and occasionally decrease in size. In the absence of strict inclusion criteria, one tumor turned out to be a craniopharyngioma in the series reported on by Donovan and Corenblum. Investigators in a Japanese multicenter study divided incidentally found pituitary lesions into eight categories that included pituitary adenomas and Rathke cleft cysts. Note, however, that researchers in that study may have misclassified Rathke cleft cysts as pituitary adenomas, which could explain the finding that as many as 10% of the pituitary adenomas decreased in size during follow-up examination. Differences in imaging modalities—that is, the use of CT or MR imaging—may also explain the discrepant findings. Magnetic resonance imaging provides better three-dimensional depictions of pituitary adenomas than does CT and facilitates a more accurate evaluation of changes in tumor size. The parameters used for evaluating size can also affect the results. Although the tumor volume can be calculated using sophisticated computer methods, such tools tend to be impractical for dealing with large num-

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**Fig. 6.** Coronal (a) and sagittal (b) MR images obtained in a 74-year-old man, demonstrating a pituitary adenoma measuring 18 mm in height with slight compression of the chiasm. Follow-up coronal (c) and sagittal (d) MR images were obtained 26 months postdiagnosis, 1 day after injection of an LHRH analog, which elicited severe headache, showing an increase in tumor size and intratumoral hemorrhagic infarction.
bers of MR images. We used tumor height as the indicator of tumor size because vertical growth is the most important predictor of the time at which impingement of the optic chiasm necessitates surgical decompression. Lundin and Pedersen\(^8\) reported that tumor height is well correlated with changes in the volume of prolactinomas in patients treated with bromocriptine. Because the definition of "enlargement" also plays a role in follow-up studies, we regarded enlarged tumors as those whose height was 110% of the height measured on initial examination. Authors of previous studies have not defined the standard used for recording tumor enlargement.

Regarding the likelihood for the enlargement of nonfunctioning pituitary adenomas, Tanaka, et al.,\(^3\) reported that tumor doubling times in patients older than 60 years of age were much longer than those in younger patients. In the present study, patient sex, age, initial tumor size, and presence of intratumoral cysts had no effect on the propensity of the adenomas to enlarge.

Pituitary apoplexy occasionally results in serious permanent morbidity, including visual impairment, and can result in hormonal deficits even in patients treated with early surgical decompression.\(^4,16,28\) In the course of 62 months in our study, pituitary apoplexy developed in four (9.5%) of 42 patients, and all suffered persistent panhypopituitarism; one patient experienced permanent visual disturbance.

The incidence of pituitary apoplexy in the natural history of pituitary adenomas remains unknown and has rarely been reported in the existing follow-up studies of incidentally found pituitary adenomas.\(^8,23,27\) Apoplectic events occurred in two of 28 patients who had been observed for 5.6 years,\(^23\) and pituitary apoplexy developed in one of 16 patients with macroadenomas who had been followed up for 6.1 years.\(^8\) Authors of the Japanese multicenter study registered one apoplectic event in 115 patients with pituitary incidentalomas during a mean follow-up period of 26.9 months.\(^27\)

Although most pituitary apoplectic events occur spontaneously, head injury, bromocriptine treatment, radiation therapy, endocrine stimulation, and anticoagulation drugs

**Fig. 7.** Coronal (a) and sagittal (b) MR images obtained in a 60-year-old woman, revealing a pituitary adenoma measuring 20 mm in height without suprasellar extension. Coronal (c) and sagittal (d) MR images obtained 20 months postdiagnosis because of acute deterioration in left-sided eyesight, showing that the tumor size had increased. Note compression of the chiasm and an intratumoral fluid hematoma.
have been suggested as precipitating factors.\textsuperscript{5,6,28} The injection of a gonadotropin-releasing hormone analog has been implicated in the development of pituitary apoplexy,\textsuperscript{5} as occurred in the case of a 74-year-old man in the present study (Fig. 6). Given that the analog can abruptly increase the metabolic activity in these tumors, the resulting insufficiency in the blood supply could precipitate massive tumor infarction. We suggest avoiding the administration of anticoagulation drugs and endocrine stimulating hormones in patients with untreated pituitary adenomas. Because pituitary apoplexy is a rare occurrence in patients with microadenomas,\textsuperscript{5,28} tumor size may be another significant factor. In addition to the four patients in our analysis, another four previously described patients\textsuperscript{8,23,27} who demonstrated pituitary apoplexy during the follow-up examination had harbored tumors larger than 15 mm at the time of detection.

In the present series, 20\% of the patients exhibited symptomatic enlargement of the tumor at 4 years postdiagnosis (Fig. 4). Furthermore, 50\% of the patients in our cohort were younger than 60 years of age. Given that the current life expectancy in 60-year-old ethnically Japanese people is an additional 21.9 years in men and 27.4 years in women,\textsuperscript{19} there is a high possibility that patients with pituitary incidentaloma who are younger than 60 years of age will eventually experience symptomatic tumor enlargement.

Because pituitary incidentalomas appear to have a high incidence of enlargement in their decades-long natural course, because the occurrence of apoplexy is possible, and because incidentalomas can be safely removed through early TSS, we propose the following management strategies.

1) Surgery is recommended in younger patients who have tumors larger than 15 mm and/or lesions with suprasellar extension on initial diagnosis. 2) Other patients should undergo regular, at least annual, follow-up examinations including MR imaging studies and pituitary function screening. If MR imaging results show tumor enlargement and chiasmal compression, surgery should be considered. 3) When monitoring is the chosen course, patients with large adenomas should not receive drugs that may precipitate pituitary apoplexy. Surgery should be performed in cases in which the administration of such drugs will become inevitable.

These strategies involve two absolute requirements. First, because benign cysts including Rathke cleft cysts rarely grow and their surgical removal is usually unnecessary, patients with such lesions should not undergo surgery. Second,
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this prophylactic surgery should only be performed at specialized pituitary centers by surgeons with extensive experience in pituitary surgery. The tumors measured less than 25 mm in 37 (88.1%) of the 42 patients in our study. During the past 10 years, two of the authors (K.A. and A.T.) have performed TSS as the initial treatment in 265 patients with pituitary adenomas having that approximate size. None of these patients died of causes related to the surgery and none suffered permanent or severe morbidity such as neurological deficit, loss of vision, or permanent diabetes insipidus. The exceptions included three patients with postoperative panhypopituitarism and two with an enlarged visual field defect. Because hands-on experience increases the safety of TSS,7 we recommend that only surgeons who have performed a sufficient number of pituitary surgeries should perform the operation at eligible pituitary centers.

Conclusions

Of the incidentally detected pituitary adenomas in the present series, 20% became symptomatic during the course of 4 years. Four patients suffered irreversible morbidity as a sequela of pituitary apoplexy. We suggest that relatively large adenomas in younger patients should be surgically treated at specialized facilities because such lesions have a risk for symptomatic growth with or without intratumoral bleeding.

References


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