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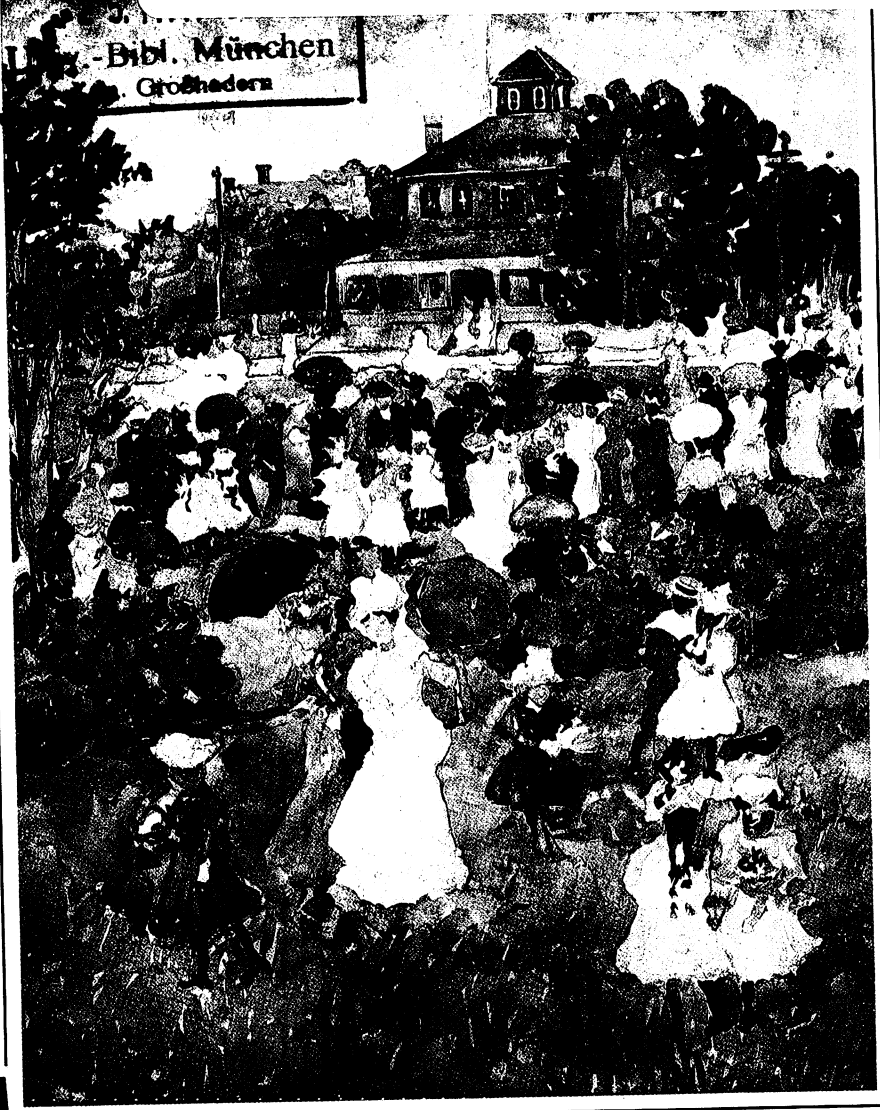

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The Journal of the American Medical Association

The 'Incidentaloma' of the Pituitary Gland

Is Neurosurgery Required?

Martin Reincke, MD; Bruno Allolio, MD; Wolfgang Saeger, MD; Jürgen Menzel, MD; Werner Winkelmann, MD

We describe a series of 18 patients with an intrasellar mass incidentally discovered by computed tomography or magnetic resonance imaging. The average size of the mass was 13 mm, with a range from 5 to 25 mm. Initial ophthalmologic examination revealed bitemporal hemianopia in 2 patients. Results of routine endocrine testing showed partial hypopituitarism in 5 patients and growth hormone hypersecretion without signs and symptoms of acromegaly in 1 patient. Four patients underwent neurosurgery. Histologically, one chondroid chordoma and three pituitary adenomas were found. In the remaining 14 patients treated conservatively, repeated computed tomography and magnetic resonance imaging revealed no significant change in tumor size at the time of follow-up (median, 22 months). Our results suggest that the "incidentaloma" of the pituitary gland is a benign condition that does not necessarily require neurosurgical intervention.

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IN 1936, Costello[1] reported in his investigation entitled "Subclinical Adenomas of the Pituitary Gland" that in a series of 1000 pituitary glands obtained from unselected autopsies pituitary adenomas occurred with the remarkable frequency of 22.5%. The tumors were unassociated with clinical signs or obvious hormonal abnormalities and remained undiagnosed during the subjects' lifetime.

Costello's investigation has been cited in numerous publications. The prevalence of subclinical pituitary adenomas has been reexamined by many subsequent investigators and was found to vary from 4.8% to 27% in unselected autopsy subjects.[2] In most cases, these adenomas were small and could only be detected by microscopy. Adenomas visible at the time of gross examination are detected less frequently. In the series of McComb et al,[2] 4 of 100 pituitary adenomas incidentally discovered at the time of autopsy were detected already by gross examination.

During the last two decades, the introduction of radioimmunoassays, new radiological procedures, and microsurgical techniques have allowed early diagnosis and removal of small pituitary adenomas. However, even today, pituitary adenomas are a common incidental finding at the time of autopsy.[3,4] With wider application of computed tomography (CT) and magnetic resonance imaging (MRI), pituitary masses will be detected incidentally during patients' lifetimes in increasing frequency. The diagnostic and therapeutic approach to patients with "incidentalomas" of the pituitary gland has not yet been established. We, therefore, present herein the findings of 18 patients with a subclinical pituitary mass incidentally discovered by CT or MRI.

PATIENTS AND METHODS

Since 1980, we studied 27 patients (21 female and 6 male) with an intrasellar mass incidentally discovered by CT or MRI (*incidentaloma*), which was defined as follows: (1) the patient underwent CT scanning (or MRI) for evaluation of an unrelated disease, and (2) the patient did not complain of symptoms associated with a sellar mass (visual disturbance, symptoms of hypopituitarism, or anterior pituitary hormone excess). Headache as an isolated symptom was considered to be nonspecific if the life profile of it was chronic, recurrent, and unassociated with other important signs. Patients with headache of increasing frequency and intensity were excluded. Patients with a primary parasellar or suprasellar mass or with the empty-sella syndrome were not included in the study.

Of the 27 patients with an incidentaloma of the pituitary gland, 9 cases were excluded from this study for the following reasons: 6 patients were unavailable for follow-up, 1 patient had suspected

From the Department of Medicine II, University of Cologne, Krankenhaus Merheim, West Germany (Drs Reincke and Allolio and Prof Dr Winkelmann); Department of Pathology, Marienkrankenhaus Hamburg, West Germany (Prof Dr Saeger); Department of Neurosurgery, Krankenhaus Merheim, Cologne, West Germany (Prof Dr Menzel).

Reprint requests to Department of Medicine II, Krankenhaus Merheim, Ostmerheimer Str 200, 5000 Köln 91, West Germany (Dr Reincke).

Table 1.—Clinical, Radiological, and Biochemical Characteristics of Four Patients With an 'Incidentaloma' of the Pituitary Gland That Required Neurosurgery*

Patient/ Age, y/ Sex	Complaint (Reason for CT)	Maximum Tumor Diameter, mm	Surgery	Endocrine Function		Visual Acuity		Histology	Immunostaining
				Preoperative	Postoperative	Preoperative	Postoperative		
1/55/F	Concussion	25	Transfrontal	Hypopituitarism (LH, FSH)	Hypopituitarism (C, TSH, LH, FSH)	Bitemporal hemianopia	Bitemporal hemianopia	Chondroid chordoma	. . .
2/64/M	Cerebrovascular disease	25	Transfrontal	Hypopituitarism (LH, FSH)	Hypopituitarism (C, TSH, LH, FSH)	Bitemporal hemianopia	Bitemporal hemianopia	Chromophobic pituitary adenoma	LH†, FSH†
3/66/M	Epilepsy	20	Transfrontal	Normal	Normal	Normal	Left hemianopia	Oncocytic pituitary adenoma	FSH‡, TSH‡, α-subunit§
4/35/M	Cervical myelopathy	17	Transsphenoidal	GH hypersecretion	Normal	Normal	Normal	Acidophilic pituitary adenoma	GH‡, PRL†, TSH†

*CT indicates computed tomography; LH (luteinizing hormone), FSH (follicle-stimulating hormone), C (corticotropin), and TSH (thyrotropin [thyroid-stimulating hormone]), hormone deficiencies in patients with hypopituitarism; GH, growth hormone; and PRL, prolactin.
†Less than 10% of tumor cells stained.
‡Greater than 50% of tumor cells stained.
§Ten percent to 50% of tumor cells stained.

Table 2.—Clinical, Radiological, and Biochemical Data of 14 Patients With an 'Incidentaloma' of the Pituitary Gland Treated Conservatively*

Patient/ Age, y/ Sex	Complaint (Reason for CT)	Maximum Tumor Diameter, mm		Endocrine Function	Follow-up, mo
		First CT	Last CT		
5/65/F	Concussion	22	25	Hypopituitarism (LH, FSH)	19
6/68/M	Cerebrovascular disease	20	20	Normal	20
7/61/F	Headache	16	15	Hypopituitarism (LH, FSH)	42
8/59/M	Cluster headache	14	20	Normal	20
9/56/M	Vertigo	14	14	Hypopituitarism (LH, FSH)	48
10/32/F	Psychiatric disorder	12	12	Normal	48
11/27/F	Headache	11	11	Normal	17
12/15/F	Epilepsy	9	9	Normal	29
13/19/F	Concussion	8	8	Normal	12
14/22/F	Syncope	8	4	Normal	14
15/24/F	Headache	8	8	Normal	17
16/43/F	Vertigo	8	8	Normal	24
17/37/F	Psychiatric disorder	5	5	Normal	20
18/44/F	Headache	5	9	Normal	96

*CT indicates computed tomography; and LH (luteinizing hormone) and FSH (follicle-stimulating hormone), hormone deficiencies in patients with hypopituitarism.

pituitary hyperplasia caused by primary hypothyroidism, and 2 patients had normal CT scans at the time of follow-up, suggestive of artifacts that imitated a pituitary tumor in the initial scans.

In the remaining 18 patients, complete medical histories were recorded and physical examinations given initially and during follow-up. In addition, ophthalmologic examinations, including Goldman and computed perimetry, and routine pituitary function testing[5] were performed. Assessment of the hormonal status included determination of baseline (and stimulated) hormone concentrations of plasma corticoptropin and serum cortisol (corticoptropin-stimulation test, overnight metyrapone test, and since 1986 corticotropin-releasing hormone stimulation test), thyrotropin (thyroid-stimulating hormone), triiodothyronine and thyroxine (thyrotropin-releasing hormone stimulation test until 1988), prolactin (thyrotropin-releasing hormone stimulation test), luteinizing hormone and follicle-stimulating hormone (gonadotropin-releasing hormone stimulation test), testosterone, growth hormone (GH), somatomedin C. α-Subunit was not measured. Follow-up studies were done every 12 months and earlier in patients with large tumors.

Plasma corticotropin levels were determined by radioimmunoassay after extraction with microfine precipitated silica granules as described previously.[6] Cortisol, prolactin, thyrotropin, triiodothyronine and thyroxine, luteinizing hormone, follicle-stimulating hormone, GH, and somatomedin C levels were measured by radioimmunoassay or immunoradiometric assay with commercially available reagents.

Sections of tumor tissue were examined by light microscopy using conventional and immunocytochemical techniques described previously.[7] Using the peroxidase-antiperoxidase method on paraffin-embedded sections, the following commercial primary antibodies were tested: anticorticotropin, anti-GH, antiprolactin, antithyrotropin, anti–follicle-stimulating hormone, anti–luteinizing hormone, anti–α-subunit.

High-resolution CT of the pituitary fossa in 2-mm sections was performed after intravenous administration of contrast material with second- and third-generation scanning machines (Siemens Somatotom DR1 and DR2, Munich, Germany). Reformatting of multiple axial images was obtained in all patients; thin-section coronal scans were obtained in 10 patients.

Since 1987, in addition to CT, magnetic resonance images in the coronal and sagittal views were obtained in eight patients at 1.0 T (Siemens Magentom 1.0T, Munich, Germany). Both T_1- and T_2-weighted spin-echo pulse sequences were acquired before and after the administration of gadolinium–diethylenetriaminepentaacetic acid.

RESULTS

Clinical data of the patients are summarized in Tables 1 and 2. In 17 patients, the pituitary mass was discovered by CT and in patient 4 by MRI. Patients' ages ranged from 15 to 68 years at the time of admission. The reasons for CT scanning (or MRI) were headache of chronic pattern (n=3), cluster headache (n=1), cerebrovascular disease (n=2), psychiatric disorders (n=2), vertigo (n=2), epilepsy (n=2), concussion (n=2), and other causes (n=4). All female patients except for the postmenopausal women had regular menses. None of the male patients com-

plained of loss of libido.

On coronal CT scans, an intrasellar soft-tissue mass greater than 10 mm in maximum diameter was identified in 11 patients (range, 11 to 25 mm) (Fig 1). Enhancement characteristics were variable, with uniformly isodense lesions (5 patients), uniformly hypodense lesions (1 patient), and mixed-density lesions (5 patients) encountered relative to the adjacent cavernous sinus. Seven tumors extended into the suprasellar region. Magnetic resonance imaging was available in 6 of these patients. In 2 patients (patients 1 and 2) with bitemporal visual field defects, the chiasm could not be discerned from the tumor by MRI. Displacement of the optic nerve was noted in patient 3, who had normal visual acuity.

In seven patients, pituitary gland CT scans showed a small lesion (diameter, <10 mm) within the sella turcica. In five of these patients, the sella cavity was almost completely filled by homogeneously enhancing soft tissue, with a convex upper contour of the gland. The two other patients had a small, hypodense lesion within the pituitary gland that was clearly distinguished from the normal enhancing parenchyma. Neither suprasellar nor parasellar extension nor sellar floor erosion was seen.

Goldman or computed perimetry revealed normal visual fields in 16 patients. Two patients showed a bitemporal visual field defect in the superior quadrant. The results of pituitary function testing was normal in 13 patients. Patients 1, 2, 5, and 7 had partial hypopituitarism (secondary hypogonadism). Patient 3 showed elevated baseline levels of GH and elevated somatomedin C concentrations without signs and symptoms of acromegaly. The GH concentrations were not suppressed to less than 2 μg/L during oral glucose tolerance testing and rose paradoxically after protirelin administration.

In 4 patients, (Table 1) neurosurgery was performed for the following reasons: visual field defects in patients 1 and 2, displacement of the chiasm by the tumor demonstrated by MRI in patient 3, and biochemical evidence of acromegaly in patient 4. In all cases, complete removal of the tumor was achieved by the transfrontal (n = 3) and transsphenoidal (n = 1) route, respectively. Histologically, a chondroid chordoma and three pituitary adenomas were found. Immunohistochemical studies showed strong GH immunoreactivity in patient 4, follicle-stimulating hormone and thyrotropin immunoreactivity in patient 3, and luteinizing hormone and follicle-stimulating hormone immunoreactivity in a few scattered cells in patient 2.

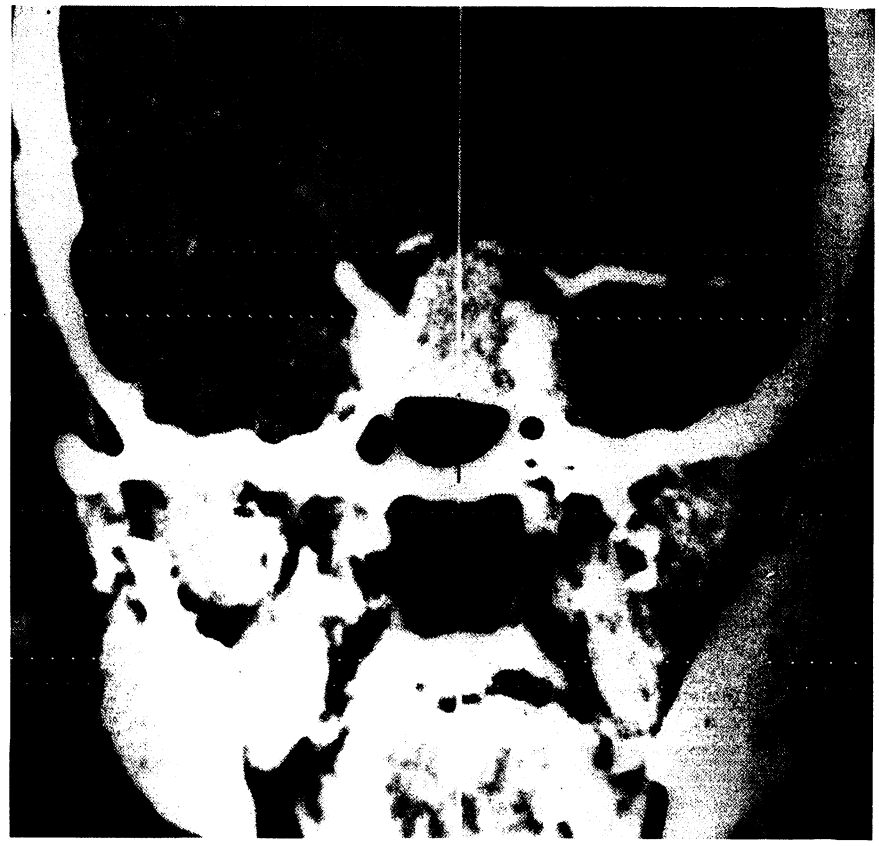

Fig 1.—Initial coronal computed tomographic (CT) scan of patient 5 showing a large pituitary mass (maximum diameter, 22 mm) with suprasellar extension. The lesion was incidentally discovered by CT after head trauma and was completely asymptomatic.

Postoperatively, complete hypopituitarism that required replacement therapy developed in patients 1 and 2. Patient 4 had normal baseline GH levels that were suppressible to less than 2 μg/L during the oral glucose tolerance test. Patient 3 had evidence of a left temporal visual field defect; visual field defects were unchanged in patient 2 and worse in patient 1. Follow-up studies were uneventful in all patients 12 to 24 months after surgery.

During the follow-up period of the 14 patients who were treated conservatively (median, 22 months; range, 11 to 96 months), no change in tumor size occurred in 10 patients. Three patients had evidence of tumor growth (patients 5, 8, and 18). Patient 14 showed tumor regression. Visual acuity remained intact in all patients. The results of endocrine follow-up studies were unchanged in 13 patients. Patient 5 had a further decrease of serum gonadotropin levels, but thyrotropin and corticotropin secretion remained intact. In 4 additional patients (patients 5, 8, 9, and 18), transsphenoidal surgery was considered because of tumor growth or hypopituitarism. However, 3 patients refused to undergo neurosurgical intervention. The fourth patient was ineligible for surgery because of severe pulmonary disease.

COMMENT

In our report, we describe 18 patients with an incidentally discovered sellar mass. In 11 patients, the lesion was greater than 10 mm in diameter. However, only 2 of the patients had visual field defects, and only 5 patients (28%) had partial hypopituitarism. In 4 patients (22%), neurosurgery was performed. Follow-up studies in the remaining 14 patients showed tumor growth in 3, whereas in the majority the lesions remained unchanged. To our knowledge, this is the first report of patients with an incidentaloma of the sellar region that provides complete clinical, biochemical, and follow-up data.

We included patients who complained of chronic headache in our series of incidentalomas of the pituitary gland. This symptom was considered to be nonspecific and not to be caused by the tumor because patients with symptomatic pituitary lesions typically complain of

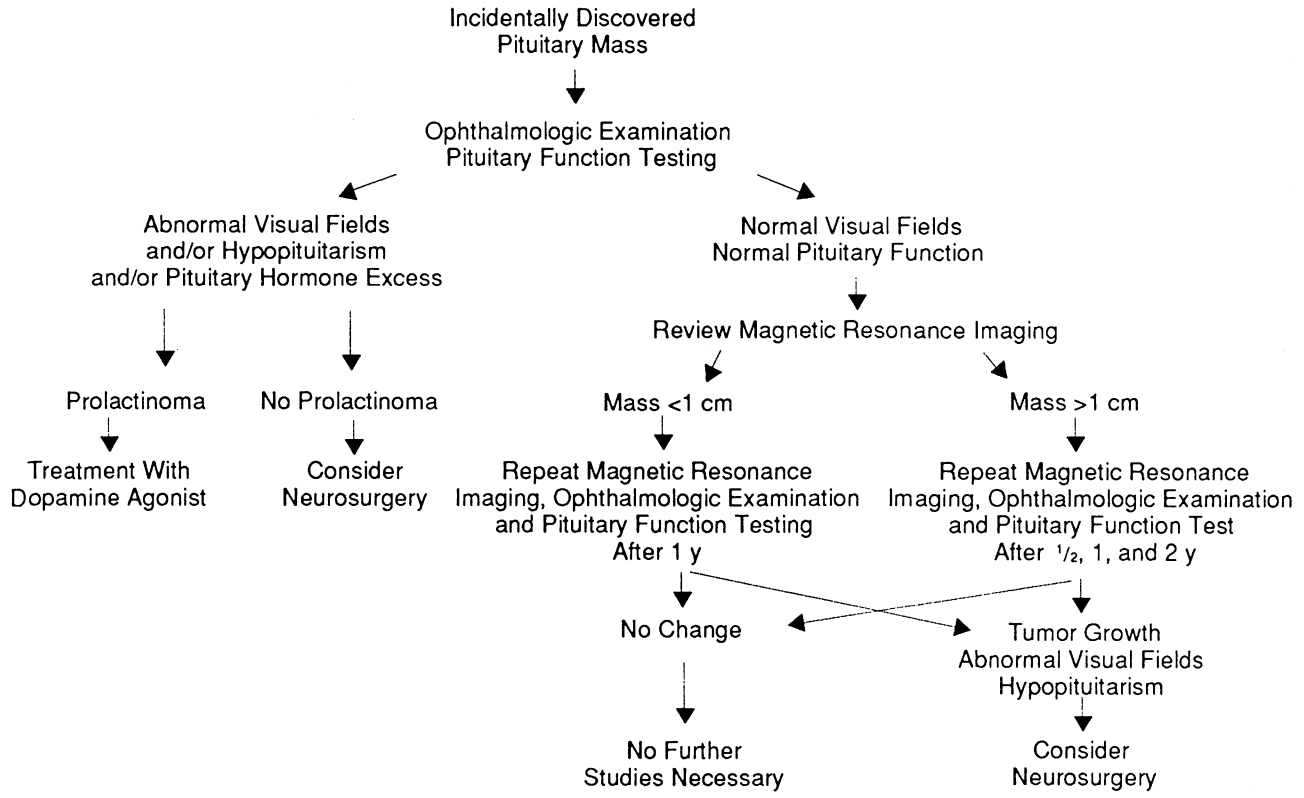

Fig 2.—Approach to the incidentally discovered noncystic mass.

headache of recent onset or increasing frequency and intensity. In addition, Cohen et al[8] reported in their large series of 100 patients with nonfunctioning pituitary adenomas that headache—the second most frequent symptom—was never observed as an isolated complaint; it was always accompanied by visual symptoms.

The pituitary region can now be easily evaluated by means of high-resolution CT[9] and MRI.[10] By CT, it is best demonstrated either directly on coronal scans or indirectly from data obtained in the axial plane and reformatted into coronal and sagittal images. The use of high-resolution CT scans for the diagnosis of pituitary tumors is well established. In the case of tumors greater than 10 mm in diameter, the mass will be easily demonstrated radiologically. However, in patients with suspected pituitary adenomas smaller than 10 mm, CT has been found to be of less value in localizing the lesion.[11,12]

Magnetic resonance imaging has been shown to be superior to CT in the evaluation of large pituitary tumors.[10,13] It is able to yield excellent anatomic presentations of the tumor and its immediate surroundings. The suprasellar extension of the tumor and the impinging of the optic apparatus and the third ventricle is more easily identified from MRI reconstructions than from CT images. In addition, MRI before and after administration of gadolinium-diethylenetriaminepentaacetic acid has been demonstrated to be more effective in the detection of microadenomas of the pituitary gland.[14] Therefore, since 1987, MRI frequently has been used by us to confirm the presence of a pituitary tumor and to define the relationship of the lesion to the surrounding anatomic structures.

Asymptomatic pituitary adenomas are a common incidental finding at the time of autopsy.[1-4] Most reported series showed an incidence of approximately 20%.[2] We believe that most of the incidentalomas in our patients represent slowly growing pituitary microadenomas and macroadenomas. No change in tumor size was noted in the majority of cases. This may be explained by the slow growth characteristics of pituitary adenoma cells.

Patients with incidentalomas of the pituitary gland should be carefully monitored for anterior pituitary hormone excess, although the majority of patients have nonfunctional pituitary tumors. In the present study, only one patient with a GH-secreting adenoma had biochemical evidence of anterior pituitary hormone excess. No prolactin-secreting pituitary tumor was detected. Immunohistochemistry revealed a gonadotroph cell adenoma in one patient whereas gonadotropin levels were normal or low in all patients. However, gonadotroph cell adenomas cannot really be excluded on this basis since serum α-subunit was not measured in our patients.

Nevertheless, subclinical masses may be caused by abnormalities other than microadenomas or macroadenomas. The differential diagnosis includes aneurysm, meningioma, and craniopharyngioma,[15] pituitary hyperplasia,[16,17] lymphoid adenohypophysitis,[18,19] pars intermedia cysts,[3] metastasis to the pituitary gland,[3,20,22] infarcts of the pituitary gland,[23] and abscesses.[3]

Aneurysm, parasellar meningioma, and craniopharyngioma sometimes mimic the CT characteristics of pituitary tumors, especially the large pituitary adenomas with suprasellar extension. However, generally they present a characteristic constellation of findings

on CT scans and MRI, which allows the differential diagnosis.[15]

It is well known that in patients with suspected microadenomas, artifacts may mimic low-density lesions on CT.[3] Earnest et al[21] stated that a significant percentage of intrasellar low-density areas, visualized on reformatted images especially, represented artifacts associated with the bones of the skull base. We excluded two patients with normal CT scans at the time of follow-up from this study in whom probable artifacts initially imitated the findings of a true pituitary tumor.

The therapeutic approach to patients with an incidentally discovered pituitary mass has not yet been established. We believe that it is rational to observe the clinical course carefully in patients with normal visual acuity and normal pituitary function. Serial CT scans or MRI, pituitary function testing, and ophthalmologic examination should be performed depending on the size of the lesion (Fig 2). Magnetic resonance imaging may be useful to confirm the presence of the mass (especially in the case of small lesions), to define the boundaries of the tumor, and to characterize its relationship to normal gland and vascular, neural, and bony structures. If the lesion shows no increase in size and endocrine and visual function remain intact, we recommend a conservative approach. However, in patients with tumor growth, loss of vision, or displacement of the optic apparatus shown on MRI or hypopituitarism or anterior pituitary hormone excess initially or at the time of follow-up, immediate neurosurgery is the treatment of choice.

In conclusion, we describe a series of 18 patients with an incidentally detected sellar mass. These lesions seem to be heterogenous in origin, however, at least some of them represent slowly growing nonfunctional pituitary adenomas. Our preliminary results suggest that in most cases the incidentaloma of the pituitary gland is a benign condition that does not necessarily require neurosurgical intervention.

Dedicated to Professor Doctor of Medicine Werner Kaufmann on the occasion of his 65th birthday.

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