ABSTRACT

Objective: To review data on epidemiology, differential diagnosis, clinical, laboratory, and imaging findings, natural history, and management of incidentally discovered pituitary lesions (pituitary incidentalomas).

Methods: A nonsystematic review was conducted, including articles indexed in Index Medicus that contained reference to incidentally discovered pituitary masses (pituitary incidentalomas).

Results: Both autopsy and sensitive neuroimaging studies (including magnetic resonance imaging) suggest that pituitary incidentalomas are common, affecting approximately 10% of the general population. Although typically small (less than 10 mm in greatest diameter) and clinically silent, some pituitary incidentalomas may be hormonally active or cause mass effects by compressing neighboring structures. In addition, a minority of these lesions may grow over time; hence, long-term follow-up is necessary. Therapeutic interventions, including dopamine agonist therapy (in the case of prolactin-secreting adenomas) or transsphenoidal resection, are indicated in the case of pituitary lesions that are hormonally active, cause mass effects, or increase in size.

Conclusion: Pituitary incidentalomas are common and constitute a heterogeneous group with regard to pathologic features, clinical, laboratory, and imaging characteristics, natural history, and growth potential. Currently available evidence suggests that many hormonally non-functioning pituitary incidentalomas causing no mass effects can be safely managed by follow-up surveillance. Nonetheless, more data are needed for further elucidation of the natural history of these lesions and for improvement in accurate and noninvasive diagnosis and in prediction of growth potential of pituitary incidentalomas. Improved understanding of the pathogenesis of this heterogeneous group of lesions may also lead to the development of novel, noninvasive therapeutic agents, rationally designed to interact with well-characterized molecular targets. (Endocr Pract. 2004;10:438-444)

INTRODUCTION

During the past several years, the widespread use of sensitive neuroimaging diagnostic techniques, including magnetic resonance imaging (MRI) of the brain, has frequently led to the detection of clinically unsuspected lesions (termed “pituitary incidentalomas”) in the pituitary gland of patients with apparently unrelated presentations, such as trauma or sinusitis (1-6). The pathologic range of pituitary incidentalomas is diverse, including pituitary cysts, adenomas, and various other lesions.

Some investigators have suggested that the term “pituitary incidentaloma” should be reserved for incidentally discovered sellar lesions smaller than 10 mm in maximal diameter (7). In the broadest (and more commonly accepted) definition, however, all incidentally discovered pituitary lesions are considered incidentalomas, regardless of size at the time of detection (3,8-10).

Despite the apparent frequency of pituitary incidentalomas, the natural history and the prognostic factors predicting tumor growth have not been clearly elucidated. Therefore, it is not surprising that the incidental detection of pituitary lesions poses major diagnostic and therapeutic challenges in clinical practice.

In the current review, data on the prevalence, pathologic features, and natural history of pituitary incidentalomas will be discussed, and controversies in the diagnostic and therapeutic approach to incidentally discovered pituitary lesions will be presented. Areas in need of further study will also be suggested.
PREVALENCE

In one study, examination of the brain by MRI in 100 normal healthy volunteers identified the presence of previously unsuspected pituitary adenomas in 10% of women and 10% of men studied (Table 1) (11). Virtually all these lesions were microadenomas, ranging from 3 to 6 mm in greatest diameter (11). A recent search of the Mayo Clinic database, however, suggested that the prevalence of pituitary incidentalomas among 4,692 MRI studies performed during the period 1995 through 1999 was 0.62% (12). The reasons for the lower prevalence of pituitary incidentalomas in the latter study are not clear.

In addition, the findings in a review of 13 autopsy studies, including almost 10,000 pituitaries, suggested that clinically unsuspected pituitary adenomas are present in more than 10% of the pituitaries examined, including more than 1,000 pituitary microadenomas (~10%) and 3 pituitary macroadenomas (~0.03%) (Table 1) (1,13-26). Individual autopsy studies, however, have provided varied estimates of the prevalence of clinically unsuspected pituitary adenomas, ranging from 1.5 to 26.7%, likely because of methodologic differences (1,13-26).

PATHOLOGY AND DIFFERENTIAL DIAGNOSIS

In an autopsy study of 1,000 unselected pituitaries, 61 pituitary incidentalomas, which were more than 2 mm in maximal diameter, were identified (27). These lesions consisted of 37 Rathke’s cleft cysts, 18 pituitary adenomas, 2 hyperplastic pituitary glands, 2 pituitary infarctions, and 2 hemorrhagic pituitaries. In this study, 70% of the lesions that were located laterally were adenomas, whereas 87% of the medially located lesions were Rathke’s cleft cysts. Of clinically unsuspected pituitary adenomas detected at autopsy, 41 to 50% show no immunoreactivity against any of the pituitary hormones, whereas 42 to 55% of these lesions demonstrate positive prolactin immunoreactivity, and 8% have positive immunoreactivity to another pituitary hormone (growth hormone, corticotropin, thyrotropin [thyroid-stimulating hormone or TSH], or gonadotropins) (1,21,28). In contrast to the high prevalence of cysts among incidentally discovered pituitary lesions, data from surgical case series suggest that pituitary adenomas account for more than 90% of symptomatic sellar masses removed through the transsphenoidal route (29).

In addition to pituitary adenomas, several diagnoses should be considered in symptomatic patients presenting with a sellar mass (Table 2) (1,29). The exact frequency of these conditions among pituitary incidentalomas has not been established. Nevertheless, the same list of differential diagnoses pertaining to a symptomatic patient with a sellar mass should also be considered in the case of a pituitary incidentaloma (Table 2). Physiologic pituitary hypertrophy should also be considered in the relevant clinical context (in healthy adolescents or young women, pregnant women, or patients with primary hypothyroidism or hypogonadism) and distinguished from an incidentally detected, pathologic pituitary lesion (Table 2) (30).

CLINICAL FEATURES

Pituitary incidentalomas are, by definition, lesions detected during the course of evaluation of apparently unrelated symptoms. Most likely, however, several of the involved patients have had subtle symptoms attributable to pituitary pathologic conditions, which were not brought to medical attention.

The detection of a sellar “macroincidentaloma” (measuring at least 10 mm in greatest diameter) should prompt the clinician to elicit the presence of symptoms attributable to local pressure (mass) effects, including headache, visual field deficits, and cranial nerve palsies (III, IV, V, and VI), as well as clinical evidence of hypopituitarism. In addition to clinical evaluation, visual field testing by perimetry should be performed in patients found to have sellar masses impinging on the optic chiasm on MRI examination.

The presence of a sellar mass should also alert the physician to seek clinical evidence of pituitary hormone excess syndromes, including hyperprolactinemia, acromegaly, Cushing’s syndrome, or thyrotropin-mediated hyperthyroidism, even though most incidentally detected pituitary adenomas are likely to be clinically silent (1,3,4).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hall et al (11), 1994</td>
<td>Magnetic resonance imaging</td>
<td>10 of 100 subjects (10%, all microincidentalomas)</td>
</tr>
<tr>
<td>Baker et al (12), 2003</td>
<td>Magnetic resonance imaging</td>
<td>29 of 4,692 patients (0.62%)</td>
</tr>
<tr>
<td>Molitch &amp; Russell (1), 1990</td>
<td>Review of 13 autopsy studies</td>
<td>1,065 microadenomas (~10.9%) and 3 macroadenomas (~0.03%) of 9,737 pituitaries</td>
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</tbody>
</table>
The natural history of pituitary incidentalomas has not been fully elucidated. Other than their size at initial manifestation, the risk factors predictive of the growth potential of incidentally discovered pituitary masses have not been well characterized.

Data from prospective studies support the association between tumor size at initial assessment and increased growth potential during follow-up (Table 3). In a prospective study by Reincke et al (31), 14 patients with incidental pituitary masses, including 7 patients with macroincidentalomas and 7 with “microincidentalomas” (less than 10 mm in greatest diameter), underwent follow-up for a mean of 22 months (range, 11 to 96). Of the 7 patients with a macroincidentaloma, 2 (29%) experienced an increase in tumor size, with gradual development of central hypogonadism in 1 of them. None of these patients underwent surgical treatment. Among the 7 patients with microincidentalomas, an increase in tumor size was noted in only 1 (14%), and a spontaneous decrease in tumor size was noted in another (14%) (31). These changes were not considered clinically significant.

In another prospective study, by Donovan and Corenblum (32), 31 patients with incidentally detected pituitary masses, including 16 patients with macroincidentalomas and 15 with microincidentalomas, had a mean follow-up period of 2.7 years (including a minimal period of 2 years). Five of the 19 patients with macroincidentalomas (26%) experienced an increase in tumor size, and in 1 additional patient from this group (5%), a decrease in tumor size was noted. In contrast, only 1 of the 31 patients with microincidentalomas (3%) demonstrated evidence of tumor growth, and in 1 additional patient from this group (3%), a decrease in tumor size was noted. In this study, none of the 6 patients with tumor growth had visual field deficits during follow-up (32).

In contrast, a retrospective survey of 239 patients with pituitary incidentalomas and a mean duration of follow-up of 26.9 months (range, 6 to 173) did not reveal an associ-
ation between tumor size at presentation of the patients and growth potential (Table 3) (34). In this study, 20 of 165 patients with macroincidentalomas (12%) and 10 of 74 patients with microincidentalomas (14%) demonstrated tumor growth during follow-up. Six of the 20 patients with macroincidentalomas whose tumors enlarged during follow-up underwent transsphenoidal surgical resection of the tumor, including 1 in whom visual field deficits had developed (as a consequence of pituitary apoplexy) (34). The apparent discrepancy between these findings and the results of the 3 aforementioned prospective studies that suggested an increased likelihood of tumor growth among patients with macroincidentalomas may reflect differences in study design (retrospective versus prospective data collection and analysis) or study population characteristics.

In addition, in the same retrospective survey (34), 23 of 115 patients with tumors thought to represent nonfunctioning pituitary adenomas (20%) demonstrated tumor growth, whereas only 5 of 94 patients with Rathke’s cleft cysts (5%) demonstrated growth of that lesion during follow-up. The retrospective nature of this study may limit the general applicability of these findings, which should be verified in a prospective investigation.

**LABORATORY DIAGNOSTIC EVALUATION**

Hypopituitarism is not uncommon in patients with macroincidentalomas (35). In one study, laboratory findings suggestive of at least one pituitary hormone deficiency were found in 6 of 10 patients with a pituitary macroincidentaloma (35). Therefore, such patients should undergo appropriate screening tests of pituitary function, including serum levels of cortisol (early morning), free thyroxine, follicle-stimulating hormone, luteinizing hormone, and total testosterone (early morning) in male patients. In contrast, hypopituitarism is unlikely in patients with microincidentalomas. In our experience with these patients, extensive evaluation of pituitary reserve is usually not necessary.

The most cost-effective approach to the laboratory investigation of hormone hypersecretion in the presence of a pituitary incidentaloma, however, has not been clearly established. Some investigators have suggested that measurement of serum prolactin is the only cost-effective test routinely indicated in patients with pituitary incidentalomas who lack clinical evidence of pituitary hormone hypersecretion (36). In the absence of extensive data on the natural history of pituitary incidentalomas, it seems reasonable to measure serum insulin-like growth factor 1 as a screening test for acromegaly, with the rationale that early detection and treatment will likely minimize the morbidity and mortality associated with this condition (37-40).

In addition, screening these patients for thyrotropin-mediated hyperthyroidism may be appropriate because this condition has been reported in 2 patients with a pituitary incidentaloma (41,42). High serum levels of free thyroid hormones in the setting of normal or high serum TSH, however, may occur in patients with thyrotropin-mediated hyperthyroidism as well as in patients with resistance to thyroid hormone. Further testing (including thyrotropin-releasing hormone stimulation and triiodothyronine suppression testing, measurement of the alpha subunit- to-TSH molar ratio, and thyroid receptor sequence analysis) is needed to distinguish between these two conditions, which also applies in the case of a pituitary incidentaloma (43).

Among patients with pituitary incidentalomas and clinical suspicion of Cushing’s syndrome, appropriate screening tests should be performed, including 24-hour urine free cortisol, 11 PM salivary cortisol, or measurement of early morning serum cortisol after administration of 1 mg of dexamethasone the night before (11 PM) (44). In contrast, the routine performance of pituitary imaging as a screening test for Cushing’s syndrome should be discouraged, in order to avoid diagnostic confusion between an incidental pituitary mass and a pituitary adenoma leading to hypersecretion of corticotropin.

### Table 3

Reported Natural History of Pituitary Incidentalomas*

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Mean follow-up (yr)</th>
<th>Lesion growth</th>
</tr>
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<tbody>
<tr>
<td>Reincke et al (31), 1990</td>
<td>14 (7 macro, 7 micro)</td>
<td>1.8</td>
<td>2 macro (29%) 1 micro (14%)</td>
</tr>
<tr>
<td>Donovan &amp; Corenblum (32), 1995</td>
<td>31 (16 macro, 15 micro)</td>
<td>6.1 (macro) 6.7 (micro)</td>
<td>4 macro (25%) 0 micro (0%)</td>
</tr>
<tr>
<td>Feldkamp et al (33), 1999</td>
<td>50 (19 macro, 31 micro)</td>
<td>2.7</td>
<td>5 macro (26%) 1 micro (3%)</td>
</tr>
<tr>
<td>Sanno et al (34), 2003</td>
<td>239 (165 macro, 74 micro)</td>
<td>2.2</td>
<td>20 macro (12%) 10 micro (14%)</td>
</tr>
</tbody>
</table>

*Macro = macroincidentalomas; micro = microincidentalomas.
It should also be noted that administration of thyrotropin-releasing hormone may provoke an increase in secretion of beta gonadotropin subunit in 73% of patients with microincidentalomas, as has been previously demonstrated in many patients with gonadotroph pituitary adenomas (45). The diagnostic accuracy of this test among patients with pituitary incidentalomas, however, has not been established.

THERAPY AND FOLLOW-UP

Therapeutic recommendations for patients with pituitary incidentalomas have been based on clinical experience and reported data from available studies on the natural history of incidentally discovered sellar masses (1,3,4,8-10,46). An issue that should be taken into consideration when the diagnosis of a pituitary incidentaloma is made known to patients is that considerable anxiety may be provoked, which, on the basis of our experience, has the potential to diminish their quality of life. Therefore, substantial time should be spent thoroughly counseling patients on the relevant diagnostic and therapeutic issues.

Patients with hormone excess syndromes should receive appropriate medical and surgical therapy (for example, dopamine agonist therapy for patients with prolactinomas or a transphenoidal surgical procedure for patients with acromegaly, Cushing’s disease, or thyrotropin-mediated hyperthyroidism).

Among patients with macroadenomas, the absence of chiasmal distortion or visual field deficits is a clear indication for therapy. If prolactinoma is the most likely diagnosis, then a trial of dopamine agonist therapy is warranted (47). In all other cases, surgical removal of the tumor, preferably by the transsphenoidal route, is indicated in order to improve vision. Even in the absence of chiasmal compression, appreciable suprasellar extension of the tumor may be an additional indication for surgical treatment in women who are interested in pregnancy. A study from Japan (48) suggested that patients with suprasellar extension of pituitary incidentalomas (grade A and even grade B in the Hardy classification) in the absence of chiasmal compression can be safely managed by follow-up surveillance. Nevertheless, the unusually high incidence of pituitary apoplexy (in 2 of 28 patients) during follow-up in that study suggests that more data are needed.

Some investigators have suggested that hypopituitarism may be an appropriate indication for surgical decompression (4). Many endocrinologists and neurosurgeons (as well as the current authors), however, do not recommend surgical treatment on this basis because tumor resection may fail to restore pituitary function or, even worse, may lead to the development of additional pituitary hormone deficiencies postoperatively.

Patients with nonfunctioning macroadenomas that are not causing mass effects, as well as patients with nonfunctioning microadenomas, may be conservatively managed by surveillance, as long as tumor growth is not detected on follow-up MRI examinations. Currently, however, data on the most cost-effective approach regarding the frequency of follow-up examinations are not available. It appears prudent to recommend an MRI examination at 6 months and annually thereafter for 2 years for patients with macroadenomas and an MRI examination annually for 2 years for patients with microadenomas, as well as at 4 years for all patients. Clearly, all patients require continued long-term follow-up beyond this period because they remain at risk for tumor growth or complications, including pituitary apoplexy (48). The optimal frequency of follow-up examinations and duration of observation, however, have not been established. A proposed algorithm for the management of patients with pituitary incidentalomas is shown in Figure 1.

FUTURE DIRECTIONS

Advances in neuroimaging have increasingly led to the early detection of generally small pituitary lesions (pituitary incidentalomas). Clearly, these lesions constitute a very heterogeneous group with regard to their pathologic features, natural history, growth potential, and response to therapy. Available data suggest that many pituitary incidentalomas that are not hormonally active and are not causing mass effects can be safely managed by observation and follow-up. Despite the abundance of information on pituitary incidentalomas provided by recent studies, however, several questions remain unanswered.

The pathogenesis and natural history of pituitary incidentalomas have not been completely understood. Moreover, the factors associated with increased risk of tumor growth have not been fully elucidated, and the optimal type, frequency, and duration of follow-up of incidentally discovered pituitary lesions have not been thoroughly investigated.

In addition to providing these data, future studies may help establish biomarkers (including laboratory tests or lesion characteristics on novel imaging studies, such as radiolabeled ligand scintigraphy or positron emission tomography) that will improve our diagnostic accuracy and ability to predict tumor growth potential reliably. It is also expected that a better understanding of the molecular pathogenesis and pathophysiology of these lesions may ultimately lead to the development of novel drug therapies for pituitary incidentalomas, rationally designed to interact with well-characterized molecular targets.

REFERENCES

Fig. 1. Suggested approach to management of incidentally discovered pituitary lesions (pituitary incidentalomas).