Incidental pituitary adenomas

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Object. Pituitary incidentalomas are a common finding with a poorly understood natural history. Over the last few decades, numerous studies have sought to decipher the optimal evaluation and treatment of these lesions. This paper aims to elucidate the current evidence regarding their prevalence, natural history, evaluation, and management.

Methods. A search of articles on PubMed (National Library of Medicine) and reference lists of all relevant articles was conducted to identify all studies pertaining to the incidence, natural history, workup, treatment, and follow-up of incidental pituitary and sellar lesions, nonfunctioning pituitary adenomas, and incidentalomas.

Results. The reported prevalence of pituitary incidentalomas has increased significantly in recent years. A complete history, physical, and endocrinological workup with formal visual field testing in the event of optic apparatus involvement constitutes the basics of the initial evaluation. Although data regarding the natural history of pituitary incidentalomas remain sparse, they seem to suggest that progression to pituitary apoplexy (0.6/100 patient-years), visual field deficits (0.6/100 patient-years), and endocrine dysfunction (0.8/100 patient-years) remains low. In larger lesions, apoplexy risk may be higher.

Conclusions. While the majority of pituitary incidentalomas can be managed conservatively, involvement of the optic apparatus, endocrine dysfunction, ophthalmological symptoms, and progressive increase in size represent the main indications for surgery. (DOI: 10.3171/2011.9.FOCUS11217)

Key Words • adenoma • incidental pituitary lesion • incidentaloma • endocrine dysfunction • transsphenoidal surgery

In clinical series, pituitary tumors are the third most common primary brain tumor, behind gliomas and meningiomas, accounting for 10%–15% of all primary brain tumors.43 At autopsy, these lesions are even more common, with an average frequency of approximately 14.4% in the general population.20

With the increase in the use of radiographic imaging, there has been a concurrent increase in the number of incidental pituitary lesions diagnosed. Generally defined as previously unsuspected pituitary lesions found on imaging performed for another reason, PIs are nevertheless not precisely delineated. While some studies include all lesions of the sella, others exclude lesions not fitting the criteria for pituitary adenoma, including Rathke cleft cysts, craniopharyngiomas, arachnoid cysts, colloid cysts, and epidermoid cysts.42,47 For the purposes of this review, we will focus on lesions most likely representing adenomas of the pituitary. Long-standing convention has classified macroincidentalomas as being 1 cm or larger and microincidentalomas as being smaller than 1 cm.

In this report, we review the existing literature regarding the incidence, natural history, workup, treatment, and follow-up of incidental pituitary lesions with a particular focus on pituitary adenomas.

Methods

A search of articles on PubMed (National Library of Medicine) and reference lists of all relevant articles was conducted to identify all studies pertaining to the incidence, natural history, workup, treatment, and follow-up of incidental pituitary and sellar lesions, nonfunctioning pituitary adenomas, and incidentalomas. In total, 34 studies, 8 reviews, and 4 consensus reports were included. Studies including patients with pituitary lesions that were symptomatic at the time of diagnosis were excluded.

Abbreviations used in this paper: ACTH = adrenocorticotropic hormone; IGF-1 = insulin-like growth factor–1; PI = pituitary incidentaloma.
Results

Radiological and autopsy study estimates of the prevalence of PIs have varied between 1% and 30%. The increased use of diagnostic imaging has yielded a dramatic increase in the number of incidentalomas diagnosed. A recent report by Raappana et al. highlighted that in the second half of an 18-year study, there was a 3-fold increase in incidentally found lesions. This accounted for the perceived increased trend in the prevalence rates of pituitary adenomas.

Despite the increased prevalence, it is believed that these data generally do not fully encompass the true frequency of these lesions. Some autopsy studies have revealed that up to 20%–25% of the general population may have a pituitary adenoma. These lesions were clinically silent and were only found incidentally postmortem through microscopic dissection of carefully sectioned samples of pituitary gland. They included mostly null cell tumors but some stained positive for prolactin, growth hormone, ACTH, thyroid-stimulating hormone, and gonadotropin hormones. It is thought that in these cases the hormone is not effectively secreted or the amount of hormone secreted is not elevated enough to be clinically significant.

Differential Diagnosis

While the majority of incidentally found pituitary lesions are adenomas, it is important to consider the large collection of other abnormalities of the sella (Appendix 1). The differential diagnosis for sellar lesions includes cystic lesions, pituitary hyperplasia, germ cell tumors, glioma, lymphoma, meningioma, metastatic tumors, and other inflammatory or vascular lesions.

Endocrinological Evaluation

The first step is to evaluate all patients who present with PI for hormone hypersecretion or hypopituitarism through a complete history, physical examination, and a basic endocrinological workup. The senior author (W.T.C.) performs an endocrinological evaluation even in asymptomatic patients. It is unknown whether downstream effects of silent somatotroph and corticotroph adenomas on cardiovascular complications, malignancy risk, and cerebrovascular disease are similar to the risk in the general population. Baldeweg et al. reported a series of 22 patients who underwent transsphenoidal resection for silent corticotroph adenomas that stained positive for ACTH. Four (18.1%) of the patients began to show signs of hypercortisolemia during follow-up, providing evidence that even silent adenomas can become secreting and that the transformation to a more aggressive tumor type should be considered in all silent adenomas. Bradley et al. reported a similar series of 28 patients who underwent transsphenoidal resection for silent corticotroph adenomas that stained positive for ACTH and compared them with patients whose nonfunctional adenomas were immunonegative for ACTH. A significant recurrence rate of 7.1% was observed in the immunopositive group compared with no recurrence in the immunonegative group.

While it is generally agreed that screening for hormone hypersecretion should be undertaken, there is currently no formal consensus on the extent of hormone screening needed. Most data on the prevalence of hormone hypersecretion come from small, retrospective studies and autopsy studies. The prevalence of clinically evident pituitary adenomas has been reported to be between 0.04 in 1000 and 1 in 1000 of the population. This broad variation likely suggests an underdiagnosis within certain communities.

Many studies have advocated obtaining a baseline serum prolactin level upon discovery of a PI. Positive staining for prolactin secretion has been seen in 11.9%–15.2% of microincidentalomas and 12.5% of macroincidentalomas in a small series of 16 patients stained positive for prolactin. While large autopsy studies have reported that 39.5% of PIs stain positive for prolactin, the clinical relevance of these findings is unclear. When assessing prolactin levels, mild elevations need to be taken in the right clinical context because of the possibility of stalk effect. Compression by lesions that block the outflow of the hypothalamus can impede hypothalamic inhibitory control on the anterior pituitary, resulting in moderate hyperprolactinemia (usually <150 ng/ml). Typically, prolactin levels 200 ng/ml or greater indicate a primary prolactin-secreting tumor. Additionally, when assessing prolactin levels in the presence of very large PIs, having the laboratory do serial dilutions of the serum sample will decrease the potential for a false-negative result due to the hook effect. Excessive levels of prolactin can prevent the formation of the necessary antibody-prolactin-signal complexes required to provide the correct reading.

Autopsy studies have shown that up to 1.8% of PIs stain positive for growth hormone. If the decision is made to evaluate for the possibility of a somatotroph adenoma, assessment of IGF-1 is typically sufficient. In the event that this is not possible, an oral glucose tolerance test can be used. Failure to suppress growth hormone levels less than 2 ng/ml after a 75-g oral glucose load indicates dysfunction along the hypothalamic-pituitary axis. In a series of 3048 autopsies, 334 pituitary adenomas were found and 13.8% stained positive for ACTH. Whereas this was previously thought to be a benign finding, reports have shown that even nonobese, normoglycemic patients with adrenal incidentalomas have glucose intolerance, insulin insensitivity, and elevated blood pressure compared with age-matched controls. Subclinical Cushing disease can be presumed to also result in the sequelae of hypertension, diabetes, and osteoporosis. Subclinical hypercortisolemia in a patient with PI should prompt a further evaluation for Cushing disease. The most commonly used screening tests for hypercortisolemia due to Cushing syndrome are the dexamethasone suppression test and 24-hour urinary free cortisol, and more recently, midnight salivary cortisol. Whether a baseline ACTH level should be measured in a patient with PI as part of the screening laboratory studies is currently a point of contention, as no systematic screening of incidentalomas for subclinical glucocorticoid excess has been reported. It is interesting to note that there have been reports of recurrence and florid hypercortisolemia in the presence of a previously resected presumed silent corticotroph adenoma.

Gonadotroph adenomas comprise approximately 10% of all pituitary adenomas, but because they overwhelmingly present as a nonfunctioning sellar mass without any
associated pituitary adenomas

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associated symptoms, screening for these entities without clinical suspicion for hypogonadism is seldom performed.\(^\text{45}\)

In patients with an initially normal endocrinological evaluation, the senior author (W.T.C.) typically repeats endocrinological laboratory studies at 1 year (Appendix 2) and then follows with additional laboratory studies thereafter only if the patient’s clinical symptoms change. Abnormal laboratory values are followed up on an individualized basis depending on the patient’s presentation.

In all patients with PIs, some consideration should be made toward the familial disorder multiple endocrine neoplasia type 1 (MEN-1). Patients who present with plurihormonal discrepancies have an increased risk of MEN-1, and further attention should be paid to obtaining a careful family history and evaluating parathyroid/pancreas function.\(^{3,41}\) Although there are no recent consensus guidelines regarding how to screen for MEN-1, such patients at our institution undergo a molecular genetic analysis for MEN1 gene mutations, as well as clinical, biochemical, and radiographic evaluations for MEN-1–associated tumors.

Evidence for the importance of screening for hypopituitarism has also come from small observational studies. Recent reports have shown rates of hypopituitarism in patients with PIs to be between 10.6% and 41.3%.\(^{3,21}\) Macroincidentalomas are much more likely than microincidentalomas to induce hypopituitarism. Reports describing the natural history of PIs smaller than 1 cm show an overwhelmingly benign course with the maintenance of normal pituitary function. Reincke et al.\(^{39}\) and Donovan and Corenblum\(^{19}\) showed that all of the patients in their combined series of 22 microincidentalomas retained normal pituitary function. Macroadenomas likely prompt altered pituitary function by direct compression on the hypothalamus, pituitary stalk, or pituitary itself. Rates of hypopituitarism in macroincidentalomas have been reported to be as high as 41.3%.\(^{22,27,44,46}\) Because of this high rate of decreased pituitary function in clinically asymptomatic patients, it is generally accepted to screen for hypopituitarism upon the discovery of macroincidentalomas. Of the endocrinopathies seen, hypogonadism, hypocortisolism, hypothyroidism, and decreased growth hormone were seen in up to 30%, 18%, 28%, and 8% of patients, respectively.\(^{3,21,22,39}\)

Radiographic Evaluation

The advent and widespread use of MR imaging has revolutionized the visualization of the sellar region. This has also led to the increase in diagnosis of PIs, namely microincidentalomas. The use of Gd contrast allows for better differentiation of the pituitary-PI interface, evaluation of abutment of the optic chiasm, and invasion into the cavernous sinus, which are all important considerations when surgery is being discussed.\(^{12}\) Coronal dynamic contrast-enhanced images are used to evaluate for nodules of decreased or delayed enhancement characteristic of macroadenomas. Thin-section or volumetrically acquired T2-weighted sequences are particularly helpful in delineation of whether the mass is intrasellar or suprasellar and whether the pituitary gland is normal. These images also demonstrate the lesional anatomy and morphology and regional mass effects on adjacent structures such as the infundibulum, optic chiasm, or internal carotid arteries. A combination of T1-weighted, T2-weighted, and contrast-enhanced sequences, usually obtained coronally, can help distinguish between a cystic lesion (for example, Rathke cleft cyst, pars intermedia, and arachnoid cyst) and the presence of hemosiderin as can be seen in hemorrhagic adenomas. Delayed postcontrast sequences can show areas of enhancement in craniopharyngioma, macroadenoma, pilocytic astrocytoma, germ cell tumor, and Langerhans cell histiocytosis. Furthermore, granulomatous processes such as sarcoidosis or tuberculosis can have additional nodular basal cistern and leptomeningeal enhancement. Menin giomas, which are common suprasellar lesions, typically demonstrate marginal peripheral dural thickening and enhancement (“dural tail”). Computed tomography scanning plays an important role in determining the presence of calcifications, which are characteristic of craniopharyngiomas, or hyperostotic changes/osseous remodeling from a meningioma. Additionally, helically acquired CT scans can provide detailed nasal cavity anatomy and can be used for stereotactic guidance.

Routine pituitary imaging performed at our institution includes sagittal T1-weighted precontrast and postcontrast images with fat saturation. In the coronal plane, precontrast T1- and T2-weighted, dynamic T1-weighted postcontrast, and delayed T1-weighted postcontrast images with fat saturation sequences are acquired. Additional whole-brain images to evaluate for extrasellar disease include axial FLAIR, T2-weighted/refocused gradient echo and diffusion-weighted imaging.

Visual Field Testing

Visual loss is one of the devastating complications associated with larger lesions with suprasellar extent. Reincke et al.\(^{20}\) monitored 11 patients with macroincidentalomas prospectively and found that 9.1% had visual field deficits and 18% had compression of the optic chiasm. In another prospective analysis of 25 patients with macroincidentalomas, initial ophthalmological evaluation yielded visual field deficits in 4.5% of patients.\(^{22}\) Dekkers et al.\(^{17}\) monitored 28 patients with newly diagnosed macroadenomas that were initially not surgically treated. Surgical treatment was eventually required in 6 (21.4%) of 28 patients who were initially asymptomatic but developed visual field deficits. Most authors propose formal visual field testing for all patients with PIs that demonstrate compression of or are adjacent to the optic chiasm on imaging.

Cost of Evaluation

Because of the frequency of incidental pituitary lesions in the general population, substantial expenses are incurred by the medical system for evaluation and monitoring even if they remain stable and no treatment is needed. A review of the experience of the University of Utah between 2002 and 2009 shows that the evaluation of a single patient with PI costs approximately $6000; this includes physicians’ fees (neurosurgeon, endocrinologist, and radiologist fees), imaging, and laboratory tests.\(^{38}\) Accounting for the average incidence of these lesions in the general population, the total cost for the US health system would be approximately $7 million in 1 year.\(^{38}\)
Natural History

Although several studies have aimed to elucidate the natural history of PIs, the resultant data have been scarce and generally of poor quality. In 2011, Fernández-Balsells et al. performed a meta-analysis of the available literature in an attempt to garner the prognostic factors involved in PI progression. Eleven primarily single-center studies were chosen. The mean follow-up time ranged from 2.3 to 8 years. Headache was the most common baseline complaint warranting obtaining MR images. The overall frequency of PIs was higher in female patients. The average event rate for all PIs was 5.8 per 100 patient-years. The incidence was significantly higher in macroincidentalomas than in microincidentalomas (12.53 vs 3.32). The incidence of pituitary apoplexy (0.6/100 patient-years), worsening of visual field deficits (0.6/100 patient-years), and onset of endocrine dysfunction (0.8/100 patient-years) were found to be low. The authors concluded that despite the thorough literature search, the available literature was scarce and not particularly helpful in predicting the natural history of PIs. Additionally, the lack of separation of nonfunctional pituitary adenomas and PIs in a few of the studies made it difficult to predict distinct incidence rates. Future studies would need to contain larger sample sizes, be prospective in design, contain clear inclusion and exclusion criteria, and have uniform follow-up.

An important paper has documented that among 42 patients with asymptomatic macroadenomas monitored for 5 years, nearly 10% developed pituitary apoplexy. This risk is important to note when counseling patients with larger tumors that are found incidentally. In addition, apoplexy may occur in microadenomas (Fig. 1). It is likely that this occurs more frequently than is recognized, but the incidence is unknown. The senior author (W.T.C.) also counsels patients about this small risk when monitoring incidental microadenomas.

Treatment of PIs

The majority of PIs do not require surgery. The data evaluating various treatments and follow-up strategies for lesions that require intervention are not substantiated by high-quality evidence; however, a few tenets appear to be generally accepted. Medical and surgical therapy is indicated when there is biochemical evidence of pituitary hypersecretion. This is well established in the literature and fortified by clinical guidelines for prolactinomas, somatotroph adenomas, and corticotroph adenomas. Untreated hyperprolactinemia can produce early and profound osteopenia in young women, in addition to infertility in both sexes. While medical therapy with prolactinomas in the form of dopaminergic agonists is attempted initially, early surgical intervention has emerged as the treatment of choice for hypersecreting somatotroph and corticotroph adenomas.

Macroincidentalomas have an established tendency to grow and cause clinically evident symptoms via compression and mass effect, with rates as high as 40% over 5 years in one study. As previously illustrated, they are almost 4 times more likely to grow as tumors smaller than 1 cm. Macroincidentalomas should be monitored closely for radiographic evidence of optic nerve and chiasm involvement, biochemical evidence of pituitary hypersecretion and hypopituitarism, and ophthalmological signs of visual field deficits, which are all indications for surgical intervention. While microincidentalomas are less likely than macroincidentalomas to grow significantly, close follow-up with history, clinical examination, biochemical testing, and radiological imaging are essential. Microincidentalomas are estimated to have a 10.6% incidence of tumor growth seen on MR imaging with follow-up periods of 8 years. Surgery is usually reserved for patients who present with rapidly enlarging tumor masses, compression of the optic apparatus, pituitary apoplexy, and evidence of hypopituitarism.

When surgery is indicated, the transsphenoidal approach has emerged as the preferred method. When performed by skilled, experienced neurosurgeons at high-volume centers, superior short-term outcomes with low morbidity and mortality have come to be expected. The senior author chooses to follow all incidental nonfunctional microadenomas that have normal documented endocrine function with a study in 1 year. If there is no demonstrable growth of the tumor, the patient is not monitored further unless symptoms develop. In larger, nonfunctional tumors, those that are 15 mm or larger, treatment is considered in younger patients, given the higher incidence of growth known to occur in these patients and the relatively higher risk of apoplexy. If the patient chooses conser-
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Conservative monitoring, yearly studies are done and the lesion is removed if growth is noted.

Practice Guidelines

In April 2011, the Endocrine Society attempted to critically analyze the data regarding the treatment of PIs and make practice guidelines regarding the evaluation, follow-up, and indications for surgery for these lesions. Each recommendation was given a strength of recommendation ("1" referred to recommendations and "2" referred to suggestions), and an assessment score on a 4-point scale regarding the quality of the evidence was used to make the specific recommendation. A 4-star assessment indicated high-quality evidence, a 3-star assessment indicated moderate quality, a 2-star assessment indicated low quality, and a 1-star assessment indicated very low quality evidence. The members of the task force reached a significant consensus, adding to the strength of these guidelines. Table 1 shows the individual recommendations, recommendation strength, and assessment score for various lesion characteristics. Strength and assessment scores for the recommendations regarding initial evaluation were strong, whereas those for nonsurgical follow-up were generally weaker. Indications for surgery were generally viewed as falling into 1 of 2 extremes, with some indications judged as recommendations with high-quality evidence but others as only suggestions with low-quality evidence. The lack of well-designed prospective studies directly comparing different treatment modalities accounts for this dichotomy.

Conclusions

Pituitary incidentaloma is a fairly common occurrence in the general population. With the increasing use of modern imaging technology, physicians are increasingly encountering these incidentally diagnosed pituitary lesions. The first step is to rule out a hypersecreting adenoma through a complete history, physical examination,

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<th>TABLE 1: Endocrine Society Clinical Practice Guidelines on PI*</th>
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and hormonal profile. The other crucial element is to ensure that the lesion is not causing significant mass effect by checking for hypopituitarism and for visual defect if the mass is abutting the optic apparatus. Although the natural history of these lesions is not fully understood, most PIs can be treated conservatively. A close clinical and radiological follow-up is of paramount importance since these lesions (mostly macroincidentalomas) can potentially grow and are predisposed to apoplexy. In accordance with the published practice guidelines, it is our practice to reserve surgery for hypersecreting adenomas (except for prolactinomas), those causing visual defect, large masses abutting the chiasm, macroadenomas with secondary hypopituitarism, and lesions with a documented increase in size.

Appendix 1: Differential Diagnosis for Sellar Masses

- Pituitary tumor
- Adenoma
- Carcinoma
- Cystic lesion
- Rathke cleft cyst
- Cerebellopontine angle cyst
- Arachnoid cyst
- Colloid cyst
- Epidermoid cyst
- Xanthogranuloma
dermoid cyst
- Pituitary hyperplasia
- Germ cell tumor
- Germinoma
teratoma
dermoid
glioma
- Lymphoma
- Meningioma
- Metastatic tumor
- Inflammatory lesion
- Pyogenic infection
- Granulomatous infection
- Sarcoïdosis
- Vascular lesion
- Aneurysm
- Cavernous angioma

Appendix 2: Endocrinological Evaluation for Pituitary Incidentalomas

Initial evaluation
- Prolactin
- IGF-1
- Growth hormone
- Fasting cortisol, serum
- ACTH
- Thyroid-stimulating hormone
- Thyroxine
- Luteinizing hormone
- Follicle-stimulating hormone, serum

If initial laboratory studies are normal, at 1 year
- Prolactin
- IGF-1
- Growth hormone
- Fasting cortisol, serum
- ACTH
- Thyroid-stimulating hormone
- Thyroxine
- Luteinizing hormone
- Follicle-stimulating hormone, serum

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Couldwell. Acquisition of data: Sivakumar. Analysis and interpretation of data: Sivakumar. Drafting the article: Sivakumar. Critically revising the article: Couldwell, Chamoun, Nguyen. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Couldwell. Study supervision: Couldwell.

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