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TOPIC REVIEW

Silent (clinically nonfunctioning) pituitary adenomas

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Abstract Silent, or clinically nonfunctioning, pituitary adenomas can arise from any anterior pituitary cell type. Some are "clinically silent" in that they result in a supranormal serum concentration of the hormonal product of the cell type from which the adenoma arose but do not cause the clinical manifestations typical of excessive levels of that hormone. Others are "totally silent" in that they result in neither hormonal excess nor clinical manifestations. Gonadotroph and null cell adenomas are the most prevalent types and are typically silent. Somatotroph and corticotroph adenomas typically cause clinical syndromes but occasionally are clinically or totally silent. Those that are silent are usually larger and grow more aggressively than those that cause clinical syndromes. Silent adenomas are usually not discovered until they become very large and cause neurologic defects, such as visual impairment, but are also often discovered incidentally when neuroimaging is performed for another reason. Silent adenomas may become, rarely, clinically apparent over time. The diagnosis of a silent pituitary adenoma begins with the detection of a sellar mass by MRI. Biochemical testing can identify the adenoma cell type in those that are clinically silent. Silent adenomas that cause neurologic deficits require transsphenoidal surgery, but those that do not can be followed by MRI. Residual or recurrent disease is treated by radiation therapy, which is usually effective in preventing further growth but results in hormonal deficiencies in about half of patients. Dopamine agonists and somatostatin analogs are usually ineffective, but occasionally have been associated with reduced adenoma size.

Keywords Pituitary adenomas · Silent pituitary adenomas · Clinically silent pituitary adenomas · Totally silent pituitary adenomas · Silent somatotroph adenomas · Silent corticotroph adenomas

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Introduction

Silent, or clinically nonfunctioning, pituitary adenomas can arise from any anterior pituitary cell type. They either do not secrete a sufficient amount of their hormonal products to cause an elevation of the serum concentration ("totally silent") or do so but the hormonal products do not result in the clinical signs or symptoms typical of that hormone ("clinically silent"). Adenomas that arise from anterior pituitary cells that secrete glycopeptide hormones, i.e. the gonadotroph and thyrotroph cells, are generally clinically silent or totally silent, although sometimes they cause clinical syndromes. Adenomas that arise from cells that secrete peptide hormones are more likely to cause clinical syndromes, but occasionally they are clinically silent or totally silent. This review describes the occurrence, clinical presentations, diagnosis and treatment of silent pituitary adenomas.

Occurrence

Silent pituitary adenomas are uncommon in the general population, although they comprise a large percentage of all pituitary adenomas.

Overall occurrence

In a cross-sectional study of the inhabitants of Banbury, UK, the prevalence was 77.6 per 100,000 inhabitants. Of these, 28 % of the total had totally silent adenomas [1]. In a retrospective study in a Finnish population, 37 % of 164 new pituitary adenomas were classified as silent in 16 years, equivalent to an incidence of approximately three new clinically silent pituitary adenomas per 100,000/2 years [2].

Gonadotroph and null cell adenomas

Gonadotroph adenomas are the most common silent pituitary adenomas, and null cell adenomas next most common. Of 3,489 pathologically confirmed pituitary adenoma specimens in the German Registry of Pituitary Tumors, gonadotroph adenomas accounted for 25.2 % [3]. Similar frequencies were found in surgical series from the United States and Taiwan, in which gonadotroph adenomas accounted for 29 % of 100 and 35 % of 339 pathologically confirmed adenomas [4, 5]. In series of silent pituitary adenomas, 43–64 % were gonadotroph adenomas [3, 6]. Null cell adenomas, defined as those that do not stain for any specific pituitary hormone by immunohistochemistry and do not result in hormonal hypersecretion in vivo, accounted for 33.7 % of silent adenomas in the German Registry of Pituitary Tumors. An additional 10.7 % were the oncocytic variant of null cell adenomas [3].

Thyrotroph adenomas

Pituitary adenomas of thyrotroph origin are uncommon, accounting for 0.4–2.4 % of pituitary adenomas in surgical series [3, 7, 8]. In a study of 1,200 pituitary adenomas, nine (0.75 %) were silent thyrotroph adenomas [7]. In two other series, 0.9 % of silent pituitary adenomas were silent thyrotroph adenomas [3, 6].

Somatotroph adenomas

In the series of 100 consecutive patients who had surgery for pituitary adenomas, 24 had somatotroph adenomas. Of these, 15 had classic or subtle manifestations of acromegaly and nine had clinically silent adenomas [4]. Somatotroph adenomas can be subclassifed based on whether they are densely or sparsely granulated by electron microscopy. Those that are sparsely granulated have been said to stain more strongly for growth hormone and to be less responsive to somatostatin analogs [9, 10]. However, in the 100 consecutive surgically excised adenomas, sparsely granulated adenomas were not obviously more common among clinically silent adenomas than among classic or subtly acromegalic [4].

Corticotroph adenomas

Clinically silent corticotroph adenomas account for 2.9–5.7 % of pituitary adenomas in surgical series [11, 12]. Among nonfunctioning adenomas in the German Registry of Pituitary Tumors, the sparsely granulated subtype 2, thought to be more aggressive, was more common (4.4 %) than the densely granulated subtype 1 (1.1 %) [3]. Some have suggested that silent corticotroph adenomas are more aggressive overall than other silent pituitary adenomas, and higher rates of multiple recurrences have been described [13]. However, retrospective studies report recurrence rates similar to those of other silent pituitary adenomas [13–15].

Lactotroph adenomas

Silent lactotroph adenomas were also uncommon in the German Registry of Pituitary Tumors. Only 1.5 and 0.15 % of silent pituitary adenomas were sparsely granulated and densely granulated lactotroph adenomas, respectively [3]. This low prevalence is consistent with the clinical observation that lactotroph adenomas hypersecrete prolactin.

Plurihormonal adenomas

Plurihormonal adenomas express multiple hormones by immunostaining. They may be clinically active or silent. In the German Registry of Pituitary Tumors, 1.8 % of silent adenomas were plurihormonal [3]. Plurihormonal adenomas are further subclassified as types 1, 2 or 3 based on ultrastructural and immunohistochemical features. By light microscopy type 1 adenomas are similar to densely granulated somatotroph adenomas. They stain for growth hormone and may also stain for other pituitary hormones. Type 2 adenomas resemble gonadotroph adenomas and stain for FSH, LH, and α-subunit, but also other hormones [3]. Type 3 adenomas stain for growth hormone, prolactin and TSH, and others. They may in fact be secretory [3, 16]. They account for just 0.9 % of pituitary adenomas and appear clinically aggressive [16].

Clinical presentations

Because they are not associated with syndromes of pituitary hormone excess, silent pituitary adenomas are often not detected until they have grown to a size sufficient to cause neurologic symptoms because of a mass effect. Another common presentation is as an incidental finding when an MRI is performed for an unrelated reason, such as head trauma. A less common presentation is for hormonal deficiencies. Although hormonal deficiencies are common when these adenomas are detected, they are usually not the

presenting symptoms. Pituitary apoplexy is also uncommon.

Neurologic presentation

Visual disturbances related to compression of the optic apparatus are common, occurring in 30.8–67.8 % [17, 18]. Visual field deficits due to compression of the optic chiasm are most common, occurring in 60.8 % of 385 patients at presentation. Extraocular muscle palsy was detected in 14.8 % [19]. The frequency with which headaches are reported at initial presentation in surgical series of silent pituitary adenomas varies considerably, from 9.7 to 60.8 % [17–19].

Incidental finding on MRI

Silent pituitary adenomas may also come to clinical attention as an incidental lesion when neuroimaging is performed for an unrelated reason. Of 721 patients with silent pituitary adenomas who had undergone surgical resection between December 1982 and December 2000, 7.9 % were initially detected as incidental radiologic findings [18]. In a retrospective study of 40 consecutive silent pituitary adenomas between 1989 and 2005, the adenoma was discovered in 37.5 % (three microadenomas and 12 macroadenomas) when brain imaging was performed to evaluate unrelated signs and symptoms [20]. It is the authors' experience that incidentally discovered adenomas are much more common than in these reports, a discrepancy that may be due to the frequency with which MRI scans are performed in the United States. An incidentally discovered silent pituitary adenoma warrants the same clinical and biochemical evaluation as an adenoma of similar size found because of symptoms, since it may result in similar neurologic and hormonal abnormalities, albeit subclinical.

Hormonal deficiencies

Deficiencies of one or more pituitary hormones can be detected in up to two-thirds of patients with silent pituitary adenomas at presentation [17], but these are usually not the cause of the presenting symptom. The most common endocrine deficiencies are of growth hormone and FSH/LH, which affect 35.8–61 % and approximately 40 % of patients, respectively [17, 19]. Premenopausal women and men with FSH/LH deficiency may present clinically with symptoms of hypogonadism. Premenopausal women and men may also present with hypogonadism due to hyperprolactinema as the result of stalk compression by the adenoma. TSH and ACTH deficiencies are less common, occurring in up to one-third of patients with silent pituitary adenomas [17, 19]. Diabetes insipidus is seen rarely (1.9 %) prior to neurosurgery [17].

Pituitary apoplexy

Pituitary apoplexy was the presenting manifestation in 3.7 % of 721 patients in one study [18] and 9.6 % of 385 patients in another [19].

Change in presentation from clinically silent to clinically apparent

A change from silent to clinically apparent has been reported for corticotroph, somatotroph and thyrotroph adenomas. Several reports have described Cushing's disease developing in patients who had previously been diagnosed with silent corticotroph adenomas [12, 21–23]. In a series of 22 pituitary adenomas with positive immunostaining for ACTH followed for an average of 4.8 years, four later developed Cushing's features [12].

Conversion from inactive to active has been reported less commonly for other pituitary adenomas. In 500 patients with pituitary adenomas followed for over 20 years, two patients who had no clinical manifestations of hormonal excess at original presentation later had regrowth accompanied by biochemical and clinical manifestations of hormonal excess. One had a somatotroph adenoma and eventually developed acromegaly, and the other had a thyrotroph adenoma and eventually developed hyperthyroidism [24].

Diagnosis

No matter what the clinical presentation—whether by neurologic symptom, incidental finding, hormonal deficiency or apoplexy—the diagnosis of a silent pituitary adenoma begins with the finding of a sellar mass by MRI. Humphrey visual field testing can determine if visual symptoms fit the pattern consistent with a sellar mass. Only biochemical testing, however, can identify some sellar masses—the "clinically silent"—as specific pituitary adenomas. Other clinically nonfunctioning adenomas—the "totally silent"—do not result in biochemical abnormalities and can be identified only if they are excised and stained immunocytochemically (Table 1).

Magnetic resonance imaging

MRI identifies the presence of a sellar mass and illustrates its size and extension into the sphenoid or cavernous sinuses and into the suprasellar cistern to elevate the optic chiasm. In two studies of patients with silent pituitary

Table 1 Frequency of silent (clinically nonfunctioning) pituitary adenomas by cell type

Adenoma type	Frequency
Gonadotroph	43–64 % [3, 6]
Null cell	44.4 % [3]
Somatotroph	9 % [4]
Corticotroph	2.9–5.7 % [11, 12]
Pluripotent	1.8 % [3]
Lactotroph	1.65 % [3]
Thyrotroph	0.75–0.9 % [3, 6, 7]

Table 2 Distinguishing clinically silent and totally silent somatotroph adenomas from those that are functioning

Classification	Acromegalic features	Serum IGF-1	GH Immunostaining
Classic	Typical	Elevated	Positive
Subtle	Mild	Elevated	Positive
Clinically silent	None	Elevated	Positive
Totally silent	None	Normal	Positive

Clinically silent adenomas cannot be recognized by a patient's appearance but can be identified by an elevated serum IGF-1 concentration

Adapted from [4]

adenomas, extension into the cavernous and sphenoid sinuses occurred in 19.2–33.2 % and 14.2–16.9 %, respectively [17, 19].

Biochemical testing

In an appreciable number of patients, biochemical testing can identify a sellar mass as a pituitary adenoma and what kind, even if there are no clinical manifestations of hormonal excess (Table 2).

Gonadotroph adenomas

Some gonadotroph adenomas can be detected preoperatively by the in vivo hypersecretion of glycoprotein hormones. In men, an elevated serum FSH concentration has been reported in 15–25 % of those with gonadotroph adenomas, with or without an elevated alpha subunit concentration [5, 25, 26]. An elevated alpha subunit concentration alone has been reported in 7 % [26]. An elevated FSH associated with a low testosterone and LH that is not elevated in a man with a large sellar mass is diagnostic of a gonadotroph adenoma. An increase in LH beta subunit in response to synthetic TRH is also diagnostic [27], but TRH is not available in the United States, and LH beta subunit assays are not readily available. An elevated testosterone and LH, with or without an elevated FSH, is also diagnostic of a gonadotroph adenoma.

Diagnosis of a gonadotroph adenoma in postmenopausal women with a sellar mass is more difficult, since they typically have high FSH and LH concentrations. However, an elevated FSH concentration associated with an LH that is low-normal or low in a woman with a large sellar mass is highly suggestive of a gonadotroph adenoma. An LH beta subunit response to synthetic TRH also occurs in women [28].

In premenopausal women, FSH hypersecretion by gonadotroph adenomas typically results in ovarian hyperstimulation, characterized clinically by oligo- or amenorrhea, ultrasonographically by very large polycystic ovaries, and biochemically by elevated FSH, normal or low LH, and markedly elevated estradiol [29, 30].

Thyrotroph adenomas

Clinically functioning thyrotroph adenomas are recognized by elevated serum thyroxine concentrations and elevated or normal TSH concentrations, but even those that do not cause an elevated thyroxine concentration sometimes can be recognized by an elevated TSH concentration. In a series of 63 patients with silent pituitary adenomas, four clinically euthyroid patients had staining for TSHβ by immunohistochemistry and elevated serum TSH levels [25].

Somatotroph adenomas

Somatotroph adenomas can be recognized even in the complete absence of any signs or symptoms of acromegaly. In a series of 100 consecutive patients with pituitary adenomas that were surgically excised, 24 had somatotroph adenomas immunocytochemically, and, of these, 8 were clinically silent, i.e. had no clinical manifestations of acromegaly but did have an elevated IGF-1 concentration [4]. It is striking that one-third of the somatotroph adenomas could not have been recognized clinically but have been recognized by IGF-1 concentration.

Corticotroph adenomas

Silent corticotroph adenomas, those that do not result in Cushing's syndrome, are well-recognized, but few reports have attempted to distinguish those that can be recognized by excessive cortisol production ("clinically silent") from those that cannot ("totally silent"). In a series of 12 patients with silent corticotroph adenomas, two patients experienced acute adrenal insufficiency following resection of their tumors, suggesting that they had secreted cortisol excessively preoperatively [31].

Treatment

Observation but no treatment

Observation but no treatment is an option for silent adenomas, even macroadenomas, that are not causing neurologic symptoms. If this course is chosen, monitoring clinically and by MRI is essential, because continued growth and development of neurologic symptoms is common. In three series of 24–115 subjects with presumed silent pituitary macroadenomas observed for an average of 42, 50 and 118 months, 50, 50 and 20 % increased in size [20, 32, 33].

Surgery

For silent pituitary adenomas causing neurologic symptoms, transsphenoidal surgery is the only treatment that has a high likelihood of ameliorating the symptoms rapidly. Recovery of pituitary hormonal function also may occur but less commonly. In a study of 279 patients with visual deficits prior to surgery, vision improved in 50.6 % postoperatively and normalized in 39.4 % [34]. A meta-analysis of 58 studies found that less than one-third of patients have postoperative improvement in pituitary hormone deficiencies [35].

Complications of transsphenoidal surgery for silent adenomas are similar to those for other pituitary macroadenomas. Perioperative mortality is low (<1 %) [35]. There is a 3 % risk of developing a new visual field deficit as a complication of surgery [35]. Sellar hematoma requiring surgical drainage occurred in 1 % and blood loss requiring transfusion in 0.4 % of 491 patients in one study [34]. There is a 3 % risk of CSF leak or fistula formation after transsphenoidal surgery, while the risk of developing meningitis is 1 % [35]. New postoperative hypopituitarism was 11 % in a meta-analysis of 31 studies [36]. In a prospective of 385 consecutive patients, transient and permanent diabetes insipidus occurred in 18.7 and 0.8 % [19].

Residual adenoma following surgery may regrow. In a meta-analysis of 19 studies of 1,614 patients followed for 42–112 months after surgery, the recurrence rate was 12 % in the 371 who had no radiographic evidence of residual adenoma following surgery and 46 % in the 600 who did [37]. In 159 patients who had an MRI 4–6 months after transsphenoidal surgery, the 10-year recurrence-free survival rate was 100 % in those who had no detectable residual, 58.3 % in those who had detectable intrasellar residual, and 23.1 % in those who had extrasellar residual [38].

Radiation therapy

The primary role of radiation therapy of silent adenomas is prevention of regrowth of residual adenomas following surgery. It is not commonly used as primary therapy, especially in the presence of neurologic symptoms, because a decrease in size may take years. Radiation from any source [X-rays from a linear accelerator, gamma radiation from ^{57}Co (gamma knife), or protons from a particle accelerator] can be used. More important, a single high dose (often called stereotactic radiosurgery) is used if the amount of tissue to be radiated is relatively small and not close to the optic apparatus; multiple small doses are used otherwise. Single high-dose radiation can be administered from any source, but fractionated radiation can be administered only from a linear accelerator or a particle accelerator [39].

Postoperative radiation decreases the likelihood of growth or recurrence of nonfunctioning pituitary adenomas [34, 35, 40, 41]. In a retrospective review of 126 nonfunctioning pituitary adenomas treated at two institutions, progression free survival was 93 % at both 10 and 15 years at the institution at which radiation was administered postoperatively and 68 % at 10 years and 33 % at 15 years at the institution where it was not [41]. In patients with nonfunctioning adenomas who demonstrated a residual postoperatively, 76 were observed only and 81 received radiation. The recurrence-free survival at 5 years was 100 % for patients who received postoperative radiation versus 39.2 % for the untreated group [34] (Fig. 1).

Some studies have evaluated single dose radiation specifically. In one study of 125 silent adenomas treated by gamma radiation, the progression free interval was 94 % at 5 years and 76 % at 10 years [42]. In another study, in 48 patients treated with gamma radiation and followed for a median of 80 months, adenoma volume decreased in 75 %, remained stable in 8 %, and increased in 17 % [43].

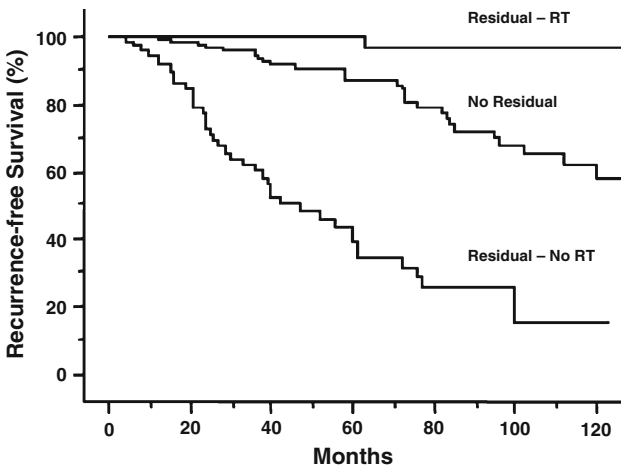

Fig. 1 Recurrence-free survival by Kaplan–Meier plots in 436 patients with silent (clinically nonfunctioning) pituitary adenomas according to the presence or absence of residual adenoma after surgery and with or without radiation therapy (RT) (adapted from [34])

Radiation has several well-documented risks, short-term and long-term. Short-term risks include fatigue, nausea, and headaches during and for up to a few months after treatment. Long-term risks include development of new pituitary hormonal deficiencies, optic neuritis and blindness, and secondary tumors.

The most common side effect is the new development of pituitary hormonal deficiencies, which may occur at least up to 10 years afterwards. The incidence varies from study to study and among the various pituitary hormones, up to as high as about 70 % at 10 years [39, 43–45].

In a series of 385 patients who had fractionated radiation over a 30-year period, therefore mostly with old techniques, the risk ratio (RR) for stroke was 1.45 for men and 2.22 for women [46]. The actuarial rate of optic neuropathy was 0.8 % at 10 years, and that of intracranial tumors was 1.9 % at 20 years.

Pharmacologic therapy

Based on the success of pharmacologic treatment of dopamine agonists for lactotroph adenomas and somatostatin analogs for somatotroph adenomas, these agents and others have been tried for silent adenomas. Although occasional patients have been reported to experience reductions in adenoma size, the success rate has been low.

Dopamine agonists

The rationale for the use of dopamine agonists in treating silent adenomas is that 55–67 % express the dopamine receptor subtype 2 (DR2) [47, 48]. In one study, 13 patients with residual or recurrent adenoma after surgery were treated with cabergoline, 1 mg/week, for 1 year. Adenoma volume decreased by 10–18 % in 7 patients, and 2 of 9 patients demonstrated improved visual field deficits [49]. In another study of treatment of 19 patients with cabergoline, 2 mg/week for 6 months, 6 had a decrease in adenoma volume of >25 %, 9 a decrease of at least 10 %, and 4 an increase [50]. In another study, reduction in the volume of residual adenoma following incomplete surgical resection, the reduction in size of the residual adenoma correlated directly with the degree of expression of DR2 in the excised tissue [48]. Further, addition of cabergoline to cultures of excised adenomas decreased cell viability more in those that expressed DR2 than in those that did not [47].

Because cabergoline has been reported to treat Cushing's disease successfully [51], it could be tried for silent corticotroph adenomas. In one patient with a recurrent silent corticotroph adenoma that expressed DR2 receptors, cabergoline decreased adenoma size appreciably [52].

Somatostatin analogs

Because some silent pituitary adenomas express somatostatin receptors [53–55], somatostatin analogs have been tried for their treatment. In a study of 39 patients with nonfunctioning adenomas who had remnants after surgery, the 26 who had positive octreoscans were treated with long-acting octreotide for a year and the 13 who had negative scans were observed only [53]. The adenoma remnant increased in 5 of 26 patients (19 %) who were treated and in 7 of 13 (54 %) who were not, but visual fields and pituitary function were unchanged in all patients [53].

Disclosure The authors declare that they have nothing to disclose.

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