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Subclinical hyperfunctioning pituitary adenomas: The silent tumors

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Abstract

Pituitary adenomas are classified by function as defined by clinical symptoms and signs of hormone hypersecretion with subsequent confirmation on immunohistochemical staining. However, positive immunostaining for pituitary cell types has been shown for clinically nonfunctioning adenomas, and this entity is classified as silent functioning adenoma. Most common in these subtypes include silent gonadotroph adenomas, silent corticotroph adenomas and silent somatotroph adenomas. Less commonly, silent prolactinomas and thyrotrophinomas are encountered. Appropriate classification of these adenomas may affect follow-up care after surgical resection. Some silent adenomas such as silent corticotroph adenomas follow a more aggressive course, necessitating closer surveillance. Furthermore, knowledge of the immunostaining characteristics of silent adenomas may determine postoperative medical therapy. This article reviews the incidence, clinical behavior, and pathologic features of clinically silent pituitary adenomas.

Keywords

pituitary adenoma; silent adenoma; clinically nonfunctioning adenoma

A. Introduction

Pituitary adenomas comprise ~15 % of intracranial neoplasms with an overall incidence of 15 to 20 per million per year. The prevalence of clinically apparent adenomas is between 2 to 2.5 per 10,000 though this may be up to 9 per 10,000 as reported(1–3). Occult adenomas are discovered in up to 25% of unselected autopsies (4). Microadenomas (less than 1 cm diameter) comprise 50–60% of these and tend not to exhibit further growth. In contrast, macroadenomas may slowly expand over years. Pituitary carcinomas comprise less than 0.2% of all pituitary tumors (5). Pituitary tumors are generally benign but can lead to morbidity from their location compressing critical structures, increasing size, and pituitary hormone over- or underexpression. Patients may experience headaches, visual disorders, and cranial nerve dysfunction from compressive effects while changes in hormone expression

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may either be due to pituitary stalk disruption or pituitary failure from compression of normal pituitary tissue.

Pituitary adenomas produce clinical features based on their specific cell type, leading to functioning adenomas. Function is defined by a clinical syndrome of hormone hypersecretion or morphological features of hormone overproduction. Prolactinomas comprise about 30 % of pituitary adenomas with a prevalence of 60–100 per million and present with amenorrhea, infertility, and galactorrhea in females and impotence or infertility in males. Somatotroph adenomas comprise 10% of pituitary adenomas with prevalence of 40–60 per million and overexpress growth hormone leading to acromegaly in adults as manifest by soft tissue and bony changes and increased risk of hypertension, cardiac disease, and diabetes. Ten percent of tumors are corticotroph adenomas which lead to ACTH hypersecretion and features of hypercortisolism. TSH secreting adenomas are rare (1% of all adenomas). Approximately 30–35% of tumors are nonfunctioning and present generally with compressive symptoms and hypopituitarism. The prevalence is 70–90 per million and include the subsets of gonadotroph adenomas, oncocytic and non-oncocytic adenomas (4).

It has become increasingly recognized that a number of pituitary adenomas present clinically as nonfunctioning adenomas but upon pathologic examination are in fact immunopositive for a pituitary hormone. This entity has become known as silent functioning adenomas. In some patients, though not clinically symptomatic, there may be detectable hormone overproduction. Silent adenomas are defined as being immunoreactive for specific pituitary hormones, manifesting ultrastructural features of a particular pituitary cell type, and/or expressing cell specific transcription factors (6, 7).

This review the epidemiology, presentation, diagnosis, pathology, and clinical behavior of subclinical functioning adenomas i.e. silent adenomas.

B. Pathogenesis of silent functioning adenomas

Role of tissue specific transcription factors

Several studies have investigated the mechanisms for the clinical silence of some functioning adenomas. Cell specific transcription factors are useful markers for identifying pituitary tumor cytogenesis (Figure 1). Anterior pituitary endocrine cell types derive from the anterior neuronal ridge (8–10) and cell type differentiation progresses from sequential expression of pituitary hormone genes (10). Tpit, a tissue-specific regulator of POMC expression, is expressed in corticotrophs and melanotrophs (11, 12) and is a specific marker of POMC-producing cells in functional corticotroph adenomas (9). Furthermore, the transcription factor NeuroD1 binds to the POMC promoter, activates POMC transcription (13), and contributes to the functional expression and differentiation of ACTH secreting adenomas as well as differentiation of nonfunctioning adenomas (14, 15). SF-1 is localized to gonadotroph cells in nonfunctioning pituitary adenomas (16). DAX-1, an orphan nuclear receptor, is also a cell-specific factor for gonadotroph cell differentiation (17) and is expressed in nonfunctioning adenomas (18). Pit-1, belonging to the homeobox family of developing regulatory proteins, activates GH and PRL genes (19) and enhances β -TSH gene transcription (20).

In silent somatotroph, thyrotroph, and lactotroph adenomas Pit-1 and GHRH-R mRNA expression by RT-PCR was similar to functioning tumor counterparts (21). Pit-1 and GATA-2 are expressed in the nuclei of all silent thyrotroph adenomas, similar to functioning adenomas (22), suggesting that the cause of the silence of these tumors occurs downstream to the Pit-1 gene in the signaling pathway leading to hormone secretion.

Examination of Tpit in silent corticotroph adenomas (SCAs) have yielded conflicting reports with one study showing Tpit positive immunohistochemistry staining in 3 of 4 SCAs (9) while others demonstrated lower Tpit mRNA and protein levels in SCAs than in functional corticotroph adenomas (23). Compared to functional corticotroph microadenomas, *POMC* and *TPIT* mRNA was variable in SCAs and macro-Cushing's though these levels correlated positively correlated in the latter groups (24).

Another study found that SCAs actually exhibit corticotroph markers, NeuroD1 and ACTH as well as gonadotroph markers, DAX-1, α -GSU, and SF-1. On the other hand, SCAs were distinct from corticotroph and gonadotroph adenomas as evidenced by absent nuclear Tpit expression while maintaining presence of cytoplasmic and nuclear SF-1, respectively (25).

Role of morphology in silent adenomas

A potential mechanism for “silencing” adenomas focuses on the ultrastructural components of these tumors. Secretory granules of silent adenomas tend to be smaller than endocrine active adenomas (6). Weaker staining LH and FSH staining in silent gonadotroph tumors may be due to abnormal Golgi apparatus leading to defective hormone packaging. The Golgi apparatus is responsible for incorporating terminal sugars to FSH which then determines serum half-life time, receptor binding affinity, biological FSH potency, and amount of releasable hormone (26, 27).

Using the reverse hemolytic plaque assay (RHPA) to visualize hormone secretion at the individual cell level, the size of the plaque was shown to correlate with the amount of hormone discharged from these cells (28). Alpha subunit, LH and FSH plaques were predominantly formed in gonadotroph adenomas though at lower levels than functioning adenomas producing GH and/or PRL. The mean plaque size was small, similar to null cell and oncocytic tumors, indicating the amount of released gonadotrophin did not differ. RHPA results correlated with hormone levels secreted into culture media (29).

To investigate the correlation between immunostaining of gonadotrophins and secreted hormone, 13 cultured gonadotroph adenomas were compared to 25 null cell adenomas. Eighty five percent of gonadotroph adenomas secreted LH/FSH *in vitro* compared to 40% of null cell adenomas. Fifteen percent of gonadotroph adenomas secreted only alpha subunit compared to 28% in null cells. The serum FSH correlated positively with *in vitro* secretion of FSH {Hanson, 2005 #297

In silent TSH adenomas, secretion of different TSH isoforms may be present or TSH secretion may be too low to lead to biologic or clinical signs of hyperthyroidism {Clarke, 2008 #61}. Also, the degree of immunoreactivity for GH may be too low in silent somatotroph adenomas (SSAs) to lead to classic acromegaly though some adenomas do indeed show diffuse GH staining as well.

Role of dysfunctional processing and biologic activity of pituitary hormones

GH release may be inhibited in silent somatotroph adenomas (SSAs) though there is no ultrastructural evidence of cytoplasmic lysosome accumulation of adenoma cells (30). These tumors may produce more than one form of GH which is immunoreactive but lacks biologic activity. However, *in vitro* studies show that cells derived from SSAs secrete GH into culture medium (30). There may be abnormal secretion given the complex processes involved in regulation of hormone extrusion from the membrane (31). There also may be defective sites of synthesis or posttranslational processing of the GH gene product (30) though some SSAs have abnormal GH dynamics on testing.

In patients with functional corticotroph adenomas, plasma ACTH levels correlate with abundance of ACTH-immunopositive cells (32). No such correlation is manifest in patients harboring SCAs (32). Individual corticotroph cells in SCAs likely secrete insufficient, or bio-inactive, ACTH molecules (32). SCAs may derive from POMC producing cells in the vestigial pars intermedia of the human pituitary (33) and the clinical SCA silence may be due to dysregulated POMC processing (34). One study showed downregulation of *POMC* and *PC 1/3* genes in SCAs compared to Cushing tumors (23).

SCAs are more similar to macro-Cushing in terms of gender ratio, age of diagnosis, invasion, recurrence, abnormalities in *POMC* processing, variability of cytological differentiation, variability of immunoreactivity of *POMC* peptides, variability in *TPIT* expression and low *galectin-3* expression (24).

Spectrum of clinical behavior and diagnosis

Several theories have been proposed to account for clinical features of these adenomas. First, SSAs described in older case reports may have indeed been diagnosed biochemically if tested according to current more rigorous criteria for acromegaly, i.e. nadir GH on oral glucose load to <0.05 mcg/L. IGF-1 assays have also evolved and need to be matched for age. SSAs may be diagnosed early in presentation and therefore do yet not exhibit clinical signs or symptoms. However, in some studies these patients have been followed for at least 8 years and did not develop acral signs (35). Another hypothesis is that as SSAs tend to present in women, who are more resistant than men to GH action than men, and thereby do not yet exhibit features of classical acromegaly.

C. Pituitary incidentalomas

Given that patients with silent adenomas do not manifest clinical symptoms to initiate a diagnostic workup, many of these adenomas are detected as incidentalomas when an imaging study is performed for a non-pituitary symptom. Autopsy studies estimate the prevalence of incidentalomas at 3–27% (36–40). A survey of 41 centers in Japan identified 506 patients with pituitary incidentalomas, neither of whom had symptoms of hormone hypersecretion. Of those who had surgery, 81% were classified as nonfunctioning adenomas (NFAs) (41). Immunohistochemistry (IHC) analysis of the 334 adenomas detected in 3048 autopsy specimens identified prolactinomas in 40%, somatotroph adenomas in 2%, and ACTH adenomas in 14% of tumors. These were mostly microadenomas without hyperfunctioning symptoms (42). A retrospective review of 41 patients who presented with incidentalomas noted 22% had hyperprolactinemia, and 15% were prolactinomas. IHC of 13/16 resected adenomas determined that 3 were gonadotroph, 4 plurihormonal, 2 GH positive, and 4 null cell adenomas (43). In a series of 11 macroincidentalomas, 1 patient had biochemical acromegaly though asymptomatic (44).

The 2010 Endocrine Society guidelines recommend screening patients with a PRL and IGF-1 measurement if diagnosed with a pituitary incidentaloma. Detecting a prolactinoma would alter management of the incidentaloma, and early detection of acromegaly may prevent later co-morbidities. However, screening for Cushing disease is reserved for those with clinical suspicion. Plasma ACTH levels are not recommended as a screening measurement for silent corticotroph adenomas (45, 46).

C. Silent subtype 3 adenomas

Many series have documented that adenomas may immuno-stain positively for more than one pituitary hormone, leading to a classification known as a silent subtype 3 adenoma, a rare tumor diagnosed by electron microscopy (EM). The initial study identified 20 patients

with this subtype who presented with macroadenomas and consequent mass effects. Women presented at younger age with hyperprolactinemia and irregular cycles. Some of the men had concomitant acromegaly or hyperprolactinemia. On histologic examination, adenomas were chromophobic with acidophilic cytoplasm and pleomorphic nuclei. A few cells were immunopositive for at least one hormone-- GH, PRL, ACTH, endorphins, or alpha subunit. EM characterized these tumors as having middle-larger sized cells with polarity and large, pleomorphic nuclei. Other diagnostic features included abundant nuclear spheridia and voluminous cytoplasm, well developed and widely distributed rough endoplasmic reticulum, and prominent Golgi. Secretory granules were spherical, measuring 50–250 nm, and unevenly distributed (47).

The clinical behavior of these adenomas tends to be more aggressive—with 1/3 of women in the initial series having recurrences (47). A follow-up study reported on 29 cases, most presenting with hyperprolactinemia and a few with acromegaly. Most tumor cells were immunonegative with a minority expressing variable reactivity for GH, PRL, TSH, alpha subunit, beta endorphin, and ACTH. Thirty-one percent of these tumors recurred (48). In 27 cases of silent subtype 3 tumors, patients presented mostly with mass effect symptoms and 8 with symptoms of hyperfunction. All tumors were macroadenomas, 81% had associated hyperprolactinemia, and 3 exhibited elevated IGF-1 levels. IHC demonstrated plurihormonal staining with EM confirming glycoprotein hormone cell differentiation and features characteristic of silent subtype 3 tumors. On postoperative follow-up, 23% of patients had recurrences (49).

D. Silent prolactinomas

Prolactinomas are the most common secretory pituitary tumor with a prevalence of 45–50 per million (2). Serum levels of PRL correlate with tumor size, with levels above 250 ng/mL consistent with a macroadenoma (50). Clinical symptoms and signs include oligo or amenorrhea or hypogonadism in men, infertility, and galactorrhea. The presentation of a prolactinoma in the absence of symptoms is rare. Of 11 patients with double pituitary adenomas, one patient presented with Cushing disease with pathologic confirmation of the corticotroph adenoma as well as a focus of a PRL positive adenoma. Additional reports noted incidental prolactinomas with Cushing adenomas (38, 51, 52). A series of 3 cases demonstrated a focus of PRL positive adenomatous cells in 3 Cushing adenomas (53). Furthermore, retrospective reviews of resected sellar lesions identified silent prolactinomas in 2% of cases (46, 54).

Knowledge of PRL positive staining may potentially provide an option for dopamine agonists in treatment of recurrent silent prolactinomas.

E. Silent TSH secreting adenomas

TSH secreting adenomas are rare, with a prevalence rate of 1/10⁶, representing 0.2–2.8% of all pituitary adenomas (55, 56). These tumors tend to be large, invasive and 1/3 may cosecrete GH and PRL (57). Clinically, patients present with mild hyperthyroidism, goiter, and mass effects. Endocrine profile shows an elevated free T4, free T3, and alpha subunit levels with nonsuppressed TSH levels. Clinically silent TSH secreting adenomas are usually detected as incidentalomas due to mass effects or as incidental findings on IHC (58). Of 12 TSH secreting adenomas, 4 patients did not present with clinical hyperthyroidism. Biochemical testing showed normal thyroid function tests in one patient, elevated TSH with normal T4 levels in 2 patients, and high T3 and T4 with inappropriately normal TSH levels in the 4th patient. Pathologic examination of the tumor confirmed immunoreactive TSH and alpha subunit while EM showed small round secretory granules (59).

When 9 silent TSH adenomas were compared to 20 clinically functioning TSH adenomas, average tumor size was larger in the silent compared to functioning TSH adenomas. IHC confirmed TSH positive staining in all silent adenomas, 3 with concurrent GH staining, 1 with PRL staining, 4 with alpha subunit staining, and 2 with FSH staining. EM confirmed the silent adenomas had thyrotroph morphology with secretory granules around 200 nm along the cell membrane (22).

Of 5000 pituitary cases, 0.4% were identified with TSH secreting adenomas (n=21) based on clinical or pathologic findings. Seventy-one percent were males with average age of 46. Eighty-nine percent of the tumors were macroadenomas with a mean diameter of 31 mm. Ten patients had clinical hyperthyroidism and 4 were hypothyroid or euthyroid. Nonsecreting TSH adenomas were diagnosed in an additional 7 patients based on positive TSH immunostaining. Of the 18 available specimens, all were positive for TSH, 8 were positive for α -subunit, 10 co-stained with GH, 7 with PRL, 2 with ACTH, and 1 with FSH/LH. All were clinically silent hormone co-secretors, except for one patient with clinical acromegaly, and none had hyperprolactinemia. EM confirmed the ultrastructure to be consistent with a TSH adenoma. Postoperative TSH levels decreased in all patients. Remission was achieved in 62% with stable residual tumor in 38% (60).

Classification of these clinically silent tumors as TSH secreting adenomas may provide a role for somatostatin analogue therapy for persistent disease.

I. Silent gonadotroph adenomas

Silent gonadotroph adenomas are the most common type of clinically nonfunctioning adenoma, comprising 10% of all pituitary adenomas (7, 61, 62). They are defined as clinically nonfunctioning adenomas which immuno-stain for FSH, LH, and/or alpha subunit but do not secrete these subunits, or if secreted into circulation do not lead to hormone-related clinical symptoms (63). Most patients present with mass effect symptoms and signs, or as pituitary incidentalomas. Preoperative endocrine testing may show hypopituitarism and hyperprolactinemia secondary to stalk effect (63).

In comparison to functioning adenomas, gonadotroph adenomas tend to have less distinctive and less uniform features. However, EM studies have detected a spectrum from null cell to well differentiated phenotypes. In men, gonadotroph adenomas are composed of small cells with moderately developed cytoplasm that contains few endoplasmic reticulum and Golgi membranes, and a variable number of secretory granules. In women, cells contain highly distinctive vesicular dilatation of the Golgi complex, well developed endoplasmic reticulum with dilated cisternae, and sparse, small secretory granules (26). The honeycomb Golgi is a characteristic feature of these adenomas, though they may also be present in corticotroph adenomas (64). Another phenotype that occurs in both genders is composed of polyhedral adenoma cells, centrally placed nuclei, medium sized (up to 450 nM) secretory granules similar to normal gonadotrophs. Oncocytic change is a common feature of these adenomas as well (65).

Seventy three percent of NFAs without endocrine abnormalities may have positive immunostaining for at least one gonadotrophin subunit (the most common being β -FSH and 2nd most common being alpha subunit) (66). Pathologic examination of a large series of gonadotroph adenomas showed that all stained for at least one gonadotrophin subunit, with/without alpha subunit. Fifty nine percent of cases had moderate or greater staining for LH, 56% for FSH, 41% for alpha subunit, and 4% for TSH. The degree of staining did not correlate with plasma gonadotrophin levels or tumor size. EM in 57 cases demonstrated "male" gonadotroph adenomas in 45%, "female" subtype in 9% (all of whom were women), and null cell adenoma of the oncocytic type (35%) or nononcocytic type (11%). Three of the

women with adenomas lacked the honeycomb Golgi characteristic of “female” gonadotroph adenomas (65).

In 100 gonadotroph adenomas, there was a male predominance, 43% had loss of visual acuity, 68% had documented visual field loss, 22% had symptoms of hypopituitarism, 17% were asymptomatic, and 8% had headaches. The majority of men had loss of libido and impotence while 1 of the 4 premenopausal women presented with amenorrhea. Preoperative plasma LH and FSH levels were not elevated in women and were generally inappropriately low for postmenopausal females. In males, 36% had elevated LH levels above 10 IU/L. Hypersecretion in this study was defined as 2x upper limit of normal and was noted in 9% of males. FSH levels above 10 IU/L were noted in 42% of males with hypersecretion in 19%. Alpha subunit levels were elevated in 1 of 29 patients in whom it was measured. Biochemical hypopituitarism was documented overall in 77% of patients, with hypogonadism in 78%, hypothyroidism in 34%, adrenal insufficiency in 26% of men. Supranormal testosterone levels were not noted. Hyperprolactinemia (2–110 ng/mL) was present in 33% of patients. All tumors were macroadenomas with mean tumor diameter 25 mm, and 41% measuring >25 mm. Tumor size was unrelated to gender or secretory hormone profile. In postoperative follow-up, 24% developed new hypopituitarism while 22% of men with preoperative hypogonadism had restoration of the gonadal axis. At 5 year follow-up of 43 patients, 42% had persistent or recurrent pituitary tumor (65).

Understanding the morphology and characterization of silent gonadotroph adenomas may help predict clinical behavior. For instance, a series of 136 silent gonadotroph adenomas (64% of NFAs) identified less cavernous invasion in this group compared to other NFAs (67) which may correlate with enhanced success of gross total resection and cure.

F. Silent corticotroph adenomas

Corticotroph adenomas (~10% of pituitary tumors) are immunopositive for adrenocorticotrophic hormone (ACTH) and are associated with elevated circulating ACTH and cortisol levels leading to Cushing disease with features of hypercortisolism (68, 69). However, up to 20% of clinically inapparent corticotroph adenomas, known as silent corticotroph adenomas (SCAs), do not manifest biochemical or clinical evidence of hypercortisolism (70–72). Some SCAs may have elevated ACTH levels with normal cortisol levels (23, 24, 73–75).

Patients with SCAs present with tumor mass effects, including headaches, visual disturbances, and hypopituitarism likely due to tumor compression of normal pituitary tissue or parasellar structures (74). Pre-operative laboratory studies reveal normal cortisol levels and normal to low LH/FSH and sex steroid and normal to slightly elevated prolactin (PRL) levels (25, 70, 72, 75, 76). Up to 60% of SCAs manifest with preoperative hypopituitarism, similar to rates observed in nonfunctioning adenomas (25, 74, 75). However, cavernous sinus invasion as visualized by MRI may be more prevalent in SCAs than in nonfunctioning adenomas (67, 74, 76, 77).

These adenomas are resected usually because of mass effects, and patients are followed postoperatively for persistent or recurrent mass growth with serial MRIs, and monitored for development of subsequent hypopituitarism (25, 72, 74–76).

SCAs exhibit variable immunopositivity for ACTH ranging from low-high (24, 25) and may express ACTH to a similar degree as functional corticotroph adenomas (32). Furthermore, EM studies have shown two morphologic variants of SCAs. Type 1 adenomas are similar to functional corticotroph adenomas in that they are densely granulated basophilic tumors with abundant cytokeratin filaments. Subtype 2 adenomas are chromophobic and lack

cytoplasmic intermediate filaments (78). In addition to corticotroph features, SCAs are shown to incorporate gonadotroph elements as evidenced by the presence of honeycomb Golgi (79, 80) and increased mitochondrial density (79). Similar findings are reported in functional corticotroph adenomas (81–83).

Characterization of these adenomas as SCAs may affect clinical management of patients. SCAs consistently demonstrate a more aggressive postoperative course compared to nonfunctioning adenomas. New onset post-operative hypopituitarism has been reported in up to half of SCAs (25, 74, 75) including postoperative adrenal insufficiency (25, 70, 72, 75, 84, 85). While SCA recurrence rates of up to 57% have been documented (74–76, 86), these rates do not differ from those observed with nonfunctioning adenomas (23, 71, 86) nor have SCAs been shown to recur earlier (86) though one series demonstrated that SCAs frequently had multiple recurrences (71). A cohort analysis of 25 SCAs demonstrated that SCAs have a 63% recurrence rate compared to 38% in nonfunctioning adenomas (25). In addition, SCAs recurred five years earlier than nonfunctioning adenoma (25), in contrast to prior reports (86), and de novo recurrences are seen more frequently in patients with SCAs (25). Rarely, SCAs may transform into functional corticotroph adenomas at later stages in the natural history of the disease (76, 79, 84).

Understanding that SCAs comprise cellular and clinical features of both corticotrophs and gonadotrophs has implications for patients undergoing long-term follow-up. The diagnosis of this tumor subtype emphasizes the need for increased postoperative surveillance of SCAs for earlier detection of recurrences and hypopituitarism through rigorous pituitary reserve testing.

G. Silent acromegaly

Acromegaly is a disease of disproportionate skeletal, tissue, and organ growth. Though the incidence of acromegaly is only 5 cases per million, untreated patients face a 10 year reduction in life expectancy and doubling of standardized mortality rates due to cardiovascular, cerebrovascular, metabolic, and respiratory comorbidities (87, 88).

Silent acromegaly can be considered as either as a clinical NFA which is immunopositive for GH on surgical specimen or as biochemical acromegaly without clinical stigmata. Rather than typing silent acromegaly as a distinct entity, there may be a continuous spectrum from clinically functioning, sparsely granulated adenomas to silent somatotroph adenomas with elevated GH levels and abnormal dynamics to SSAs with normal GH levels and dynamics.

In the earliest reports of silent acromegaly, 3 patients were described without clinical stigmata of acromegaly but with elevated IGF-1 and nonsuppressed GH levels on OGTT were found on IHC to have GH positive tumors. Tumor tissue exhibited high GH levels as measured by gel chromatography. However, EM did not classify the adenomas as typical somatotroph adenomas (89). Three other patients presented with no clinical features of acromegaly and normal to slightly elevated random GH levels. While one adenoma was immunonegative for GH, the other 2 tumors were positive for GH with EM showing features consistent with sparsely granulated somatotroph adenomas. Cultured tumors released GH into the medium and appropriately responded to stimulatory and inhibitory substances. GH mRNA was detected in all 3 adenomas by in situ hybridization (30).

In a cohort of 17 silent somatotroph adenomas, one group had mildly elevated GH (n=4) and the second group had GH levels below 5 mcg/L (n=13). Immunocytochemistry confirmed tumoral GH secretion in all adenomas while five cases had intratumoral GH elevations, *in vitro* culture, and/or ISH. In the 1st group, the tumors were small, well differentiated somatotroph adenomas and were felt to be an early presentation of acromegaly while in

group 2, the tumors were larger and more poorly differentiated, thereby secreting lower GH (90).

In patients with silent acromegaly who presented with normal preoperative IGF-1 but nonsuppressed GH levels on OGTT, these adenomas were GH positive on IHC with EM features similar to sparsely granulated somatotroph adenomas. Additionally, these adenomas had positive signal for GH mRNA as assessed by in situ hybridization. Reverse hemolytic plaque assay confirmed that fewer cells secreted GH and produced less GH compared to clinically active somatotroph adenomas. Postoperatively, GH dynamics normalized. Though no correlation was found between adenoma type and serum GH and IGF-1 levels or signs/symptoms of acromegaly, the amount of GH secretion per tumor volume was lower in sparsely granulated subtypes (91).

1.1% of 620 pituitary adenomas met the following criteria for silent somatotroph adenomas as defined by a preoperative clinical presentation of nonfunctioning adenoma with either (a) positive staining for GH on pathologic specimen, (b) positive GH mRNA by in situ hybridization but negative GH immunostaining, or (c) somatotroph morphology on electron microscopy. Clinical symptoms included headache and visual disturbances, and all patients had macroadenomas with suprasellar extension. Serum GH was mildly elevated in 2/7 cases while normal in the remainder. IGF-1 levels were normal in 3/7 that were measured, and 3 patients had hyperprolactinemia. Morphological features of SSAs demonstrated that these were chromophobic adenomas with some nuclear atypia, occasional mitotic figures, Ki-67 <1%, and no p53. Immunopositivity for GH was <25% compared to the acromegaly cases. GH mRNA was detected on ISH in all SSAs, with higher signal in densely granulated compared to sparsely granulated types. Five of seven SSAs recurred after resection. The group concluded that SSAs presented at younger ages with larger, more invasive adenomas than classic acromegaly and tend to recur more often (92).

In a retrospective review of 100 consecutive cases, 24 somatotroph adenomas were subclassified as classic somatotroph adenomas (n=11) (clinical and biochemical acromegaly with GH positive adenomas), subtle acromegaly (n=4) (mild clinical symptoms, elevated IGF-1, and GH positivity), clinically silent acromegaly (n=8) (no acromegaly features, elevated IGF-1, and GH positive staining), and silent somatotroph adenoma (n=1) (no features, normal IGF-1 but GH positive staining). There was an even distribution of gender and age in clinically silent somatotrophs. All adenomas were macroadenomas and expressed GH in variable patterns on IHC. One adenoma was densely granulated and the others either sparsely or intermediate granulated. The silent somatotroph adenoma was intermediately granulated. All 8 patients showed a decrease in serum IGF-1 levels after resection of the adenomas, or on treatment with somatostatin analogues (93).

Despite normal preoperative GH dynamics, some patients with silent acromegaly manifest abnormal GH dynamics after surgery. Two patients with GH positive tumors had normal IGF-1 levels pre-operatively possibly due to oral contraceptive use. After surgery, persistent biochemically active disease was unmasked (94).

Clinical presentation of silent acromegaly is similar to nonfunctioning adenomas. However, as up to 40% of somatotroph adenomas may co-secrete PRL, patients may indeed present with symptoms secondary to hyperprolactinemia. In a series of 17 somatotroph adenomas without acromegaly features, 13 presented with amenorrhea and/or galactorrhea associated with elevated PRL levels (90).

In 3 silent somatotroph adenomas, 2/3 of premenopausal females presented with amenorrhea and mild hyperprolactinemia, normal IGF-1 levels, and normal GH suppression on OGTT. The resected adenomas were chromophobic, acidophilic, and immunopositive for PRL and

GH. In situ hybridization confirmed positive signal for GH mRNA, PRL mRNA, and Pit-1 mRNA. These patients were also noted to have paradoxical rises in serum GH on TRH and GnRH provocation tests. Postoperatively, these paradoxical responses resolved and menses resumed (95).

Knowledge of positive GH immunostaining of silent somatotroph adenomas may change management of persistent disease after surgery by providing options to treat these patients with somatostatin analogues and/or dopamine agonists.

Practice points

- Clinically silent functioning adenomas may present with hyperfunctioning endocrine profiles even in asymptomatic patients
- Preoperative testing of pituitary incidentalomas should include measurement of PRL and IGF-1 levels
- Comprehensive immunostaining of silent adenomas for cell-specific markers may help guide medical management after surgical resection

Research agenda

- Further studies on postoperative clinical course of silent adenomas
- Trials are needed to determine if silent functioning adenomas respond to medical therapies similarly to their functioning counterparts

Summary

Silent functioning adenomas are relatively common. They are diagnosed as clinically nonfunctioning adenomas on preoperative assessment. Often they present as pituitary incidentalomas. Some patients may manifest with mild hypersecretion on biochemical testing despite the lack of symptoms. Pathologic examination of resected tissue confirms the diagnosis of silent functioning adenomas and determines the final classification of these tumors as silent subtype 3, prolactinomas, gonadotroph adenomas, silent corticotroph adenomas, or silent somatotroph adenomas. Each class of silent adenomas has a unique diagnostic and ultrastructural profile, reflective of the cell of origin (Table 1). Knowledge of the subtypes may help determine postoperative surveillance as some of these adenomas exhibit more aggressive growth. Medical therapy used in functioning counterparts may be a potential avenue of treatment for silent adenomas, though this approach has yet to be studied in future trials.

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Figure 1.

Model for development of human anterior pituitary cell lineage determination by a temporally controlled cascade of transcription factors. Trophic cells are depicted with transcriptions factors known to determine cell-specific human or murine gene expression. Adapted with permission from S. Melmed, *J. Clin. Invest.* **112**:1603–1618 (2003). doi: 10.1172/JCI200320401.

Table 1

Features of silent pituitary adenomas

	% of all adenomas	Presenting features	Imaging features	Postoperative course	IHC	EM
Silent subtype 3	0.9%	Mass effects; hyperprolactinemia	Macroadenomas	More aggressive; recurrences	GH PRL ACTH Alpha subunit endorphins	Large polar cells Pleomorphic nuclei Abundant cytoplasm Widely distributed rough ER Prominent Golgi Granules 50–250 nM
Silent prolactinomas	2%	Mass effect	Micro or macroadenoma	N/A	PRL	N/A
Silent TSH secreting adenomas	0.4%	Normal thyroid function tests	Macroadenomas; invasive	Majority in remission, stable tumor	TSH GH PRL LH/FSH Alpha subunit	Thyrotroph morphology Granules 200 nM along cell membrane
Silent gonadotroph adenomas	7–15%	Mass effects	Macroadenomas	May have fewer recurrences	FSH LH Alpha subunit	Gender specific structure Honeycomb Golgi
Silent corticotroph adenomas	3%	Mass effects	Macroadenomas, invasion	More aggressive, earlier recurrences, more hypopituitarism	ACTH	Subtype 1 Subtype 2
Silent somatotroph adenomas	1%	Mass effects; Mild ly elevated IGF-I, nonsuppressed GH	Macroadenomas, invasive	More recurrences	GH PRL	Sparsely granulated; densely granulated