



(REVIEW ARTICLE)



## Mini review of the pathogenesis, incidence, and treatment of Pituitary adenomas

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### Abstract

In this review article, we are discussing the origin of pituitary tumors. We are showing the pathological transcription factors playing role in the differentiation of the pituitary cells. We are also describing the regulation of pituitary hormone secretion, describing the incidence of pituitary tumors, and at length describe the modern treatment of them with surgery, medications, or stereotactic radiosurgery (gamma knife) as well as a combination of different treatment modalities.

**Keywords:** Pituitary Adenomas; Microadenomas; Macroadenomas; Transsphenoidal Surgery; Gamma Knife; Prolactinoma; Acromegaly; Cushing's Disease; TSH Secreting Pituitary Adenomas.

### 1. Introduction

The anterior pituitary from where the pituitary adenomas arise is formed from the Rathke pouch. The pluripotent pituitary stem cells form different anterior pituitary cells through lineage-specific transcription factors. The major proximal determinant of the pituitary cells is the protein PROP 1, which determines the transcription factors for the development of gonadotroph cell lineage- POU1F(PIT1) factor, and corticotrope cell lineage through the transcription factor TBX19. LHX3 determines the Prolactin, Growth Hormone, and TSH differentiation. PitX1 and PitX2 behave as universal pituitary regulators of all major anterior pituitary hormones [ 1,2]. The anterior pituitary secretes 6-hormones. They are under the regulation of the hypothalamus and the peripheral hormones they stimulate usually. For example, the major stimulator of Thyroid stimulating hormone (TSH) is TSH releasing hormone- (TRH), and major inhibitors are the peripheral hormones that TSH stimulates from the thyroid gland Thyroxin-(T4) and Triiodothyronine (T3). The stimulation of the Growth hormone is done by Growth hormone-releasing hormone (GHRH) from the hypothalamus and inhibition is done by somatostatin secreted also from the hypothalamus. Prolactin is stimulated by TRH and is inhibited from the Dopamine of the Hypothalamus (HT). Adrenocorticotropic Hormone (ACTH) is stimulated by ACTH releasing hormone from the hypothalamus and stimulates the production of adrenal androgens and cortisol and cortisol suppresses the ACTH. And finally, gonadotropic hormones- Luteinizing hormone (LH) stimulates the testes to produce testosterone and is suppressed by excess of testosterone and estrogens in men. In females, it has a critical role in ovulation and secretion of ovarian androgens. The follicular stimulating hormone stimulates in men spermatogenesis and the inhibin from Sertoli cells of the seminiferous tubules of the testes suppress FSH. In females, FSH plays a critical role in the development of the main follicle for ovulation and fertilization. Both hormones are under the stimulatory effect of Gonadotropin-Releasing Hormone (GnRH). Estrogens might stimulate or suppress the gonadotropin hormones in females depending on the time of the female's menstrual cycle.

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## 2. Incidence of the pituitary adenomas

One in 10 people will develop pituitary adenomas in their lifetime. Some investigations using MRI or post-mortem have found that 10-38% of people have pituitary adenomas [3,4]. They can be micro-adenomas – less than 1 cm or macro-adenomas – larger than 1 cm. The non-functioning pituitary adenomas are around 43 %, prolactin-secreting adenomas are around 40%, Growth hormone-secreting pituitary adenomas are around 11%, and ACTH-secreting adenomas are around 5%. TSH-secreting tumors or Gonadotropin hormone (GTH)-secreting adenomas are less than 1 %. Most non-functioning pituitary adenomas are GTH-secreting, but the level of the GTH secretion is not enough to cause clinical changes usually. Non-secreting pituitary microadenomas do not need to be surgically resected usually. Secretory microadenomas usually require further medical or surgical care. Macroadenomas especially if causing compressive symptoms, hormonal deficiencies or are enlarging, or secretory need surgical treatment. The exceptions are the prolactinomas which are treated usually with medications first.

### 2.1. Treatment of pituitary adenomas

For symptomatic micro prolactinomas or macro prolactinomas, therapy with a dopamine agonists (D2-receptor agonist) is the treatment of choice, not the transsphenoidal surgery (TSS)[5,6]. The goal is to restore prolactin levels to normal, with a return of eugonadal state, reducing the tumor size, preserve pituitary function, improve bone mineral density, stop galactorrhea, normalize the menstrual cycles and prevent disease progression and recurrence. Only 7-10% of micro prolactinomas will progress to macro prolactinomas.

The most common dopamine agonists for treatment of symptomatic prolactinomas are bromocriptine (2.5-15 mg taken at night or given in divided doses up to three times a day) and cabergoline (0.25-3 mg weekly dose-0.125-1.5 mg given twice weekly).

Cabergoline is the primary dopamine agonist used [7]. It is also employed in cases of bromocriptine intolerance or resistance (although if there is intolerance to oral bromocriptine in a female patient, a transvaginal formulation is available and can be tried first) [7]. The reasons for the preferential use of cabergoline over bromocriptine is the better compliance among patients (twice weekly for cabergoline versus three times a day dosing for bromocriptine), a longer half-life, a better side effect profile, a higher affinity for D2 receptors on prolactinomas, lesser resistance, and higher potency and efficacy. Cabergoline normalizes prolactin levels in patients with prolactinomas in 80-90% of cases, shrinks the tumor in 80%, leads to resolution of amenorrhea and restoration of fertility in 72%, and results in resolution of galactorrhea in 86% of patients [5,6,7]. In patients taking bromocriptine, tumor shrinkage is achieved in only 60% of patients.

In prolactinomas that are resistant to bromocriptine, switching to cabergoline is frequently effective. Resistance to bromocriptine is defined as failure of a 15 mg per day dose of the drug over at least 3 months to decrease the size of the prolactinoma by over half and the prolactin level by more than 50%. Bromocriptine resistance is also defined as a failure to restore fertility and eugonadism.

It is recommended, if the dose of cabergoline is higher than 2 mg per week, that echocardiograms be performed periodically to monitor for heart valve abnormalities [8].

In post-menopausal women with micro prolactinomas, treatment is not necessary. Similarly, in patients with micro prolactinomas who are not seeking fertility and in the absence of hypogonadism and galactorrhea, treatment with a dopamine agonist is not indicated. In these instances, however, it is necessary to continue to follow up with the patients clinically and biochemically and to perform MRI of the hypophyseal area periodically.

In pre-menopausal women with micro prolactinomas and amenorrhea who do not desire pregnancy, consider treatment with oral contraceptives as an alternative to dopamine agonists to prevent bone loss and regulate the menstrual cycles.

During pregnancy, dopamine agonists should be discontinued; the incidence of growth of micro prolactinomas during pregnancy is very low-approximately 2.4%. For macro prolactinoma especially within 5 mm of the chiasm not well responding to dopamine agonists trans sphenoidal (TSS) surgery before pregnancy is advised [9].

For men with micro prolactinomas and hypogonadism who do not seek fertility, testosterone administration without dopamine agonists will usually suffice.

There are giant macroprolactinomas. Again, the first line of treatment is with dopamine agonists. The reason is that if surgery is done frequently there is recurrence of the macro prolactinoma and if there is a giant tumor a lot of complications during surgery can happen. Surgery in terms of transsphenoidal resection of prolactinomas usually is done if there is no effect of dopamine agonists, intolerance to them, in patients who have a rare cerebrospinal leak while undergoing dopamine agonist therapy, as well as in patients who have other, co-secreting hormones and those in whom long-term medical therapy is not feasible as well as before pregnancy in macro prolactinomas if the tumor is not responding to medical therapy as discussed above [10,11,12].

Rarely when on dopamine agonist large macro prolactinomas shrink, and from the eroded from them sphenoidal sinus leaks cerebrospinal fluid from the nose of the patient. Surgery is needed to avoid infections like meningitis.

For giant macroprolactinomas not responsive to medications, radiotherapy, or surgery the alkylating agent Temozolomide is used [10,11,12]. Also, for resistant cases, radiotherapy with a gamma knife is used.

TSS is the primary treatment for pituitary tumors secreting excess Growth hormone (GH) [13,14].

The main factor for success is the experience of the surgeon. It needs to be found a surgeon who does 3-5 pituitary adenoma surgeries per week to assure better results.

If there is severe pharyngeal thickness or high cardiac output heart failure medical therapy can be started only without surgical intervention.

Surgical cure rates for acromegaly due to a growth hormone-secreting micro adenoma vary between 80- 90% and 50-60% for macro adenomas [13,14]. If initial surgery is not successful and there is a residual intrasellar tumor, and this tumor is small and has not invaded the sinuses a second surgery is recommended [13,14].

Medical therapy for acromegaly is administered if the disease persists after TSS or in patients with contra indications to surgery, severe pharyngeal thickness, high cardiac output heart failure, if the patients are poor surgical candidates or as per patients' preference. Patients with the persistent disease will demonstrate elevated Insulin Growth factor 1(IGF-1) six – weeks after the TSS, random or 2 – hours after 75 grams glucose oral glucose tolerance test growth hormone levels of more than 1 mcg/L- 3- months after TSS.

In addition, due to the delayed effect of stereotactic radiosurgery, medical therapy can be employed as adjunctive treatment to this procedure.

Before medical therapy, the surgical debulking of the tumor can help achieving favorable results.

The success of the medical treatment depends on the pretreatment IGF-1 level, random Growth hormone (GH) level, the size of the tumor, and the granularity of the tumor.

The injectable somatostatin receptor ligands (iSRLs) controlled acromegaly in around 50% of patients, as measured by normal IGF-1, and in 60% of patients when assessed by a random growth hormone level of less than 2.5 mcg/L. Both a normal IGF-1 level and a random growth hormone level of less than 2.5 mcg/L were achieved in 40% of patients in studies using octreotide long-acting release (LAR) and lanreotide auto gel [15,16]. The response to the iSRLs octreotide LAR and lanreotide auto gel, as well as to oral octreotide, has been found to be better in tumors containing dense granules. Such tumors possess more somatostatin receptor-2 (SST2) granules and have little somatostatin receptor 5 (SST5) granulation.

If the GH excess is mild- IGF-1 less than 2.5 times normal for the gender and age of the patient Cabergoline twice a week might be used with success rate around 30-40% [ 17].

Tumors which do not respond to octreotide auto gel or Lanreotide LAR which contain SST5 granules-sparsely granulated adenomas secreting excess GH respond well to injectable (iSRL) Pasireotide in 40% of the cases [15].

Finally, if the GH secretion does not improve the iSRLs might be switched from one to another, or if there is partial response the dose can be increased and combination therapy with Cabergoline or Pegvisomant used.

iSRLs decrease the size of GH-secreting tumors by 59% [15,16].

The growth hormone–receptor antagonist pegvisomant at 20 mg subcutaneously (SC) once daily normalized IGF-1 in 90% of patients with acromegaly. However, it is necessary while using this drug to monitor the size of growth hormone–secreting microadenomas, since pegvisomant was associated with the enlargement of these lesions in 2.2% of patients [18]. Close monitoring of aspartate transaminase (AST) and alanine transaminase (ALT) was found to be necessary on a monthly basis in the first 6 months and periodically thereafter, with 1.2% of patients having demonstrated elevations of these enzymes to over three times the normal levels.

Used together, pegvisomant, with doses of up to 160 mg SC once a week, and iSRLs, administered once monthly, normalized the IGF-1 level in 95% of patients with acromegaly [13].

Other treatment modality which can be used at any time is radiation therapy with a gamma knife [19]. The response is slow and usually necessitates medical therapy as well. It is primarily used when there are contraindications to surgical therapy.

Cushing disease is best treated with surgical resection of the micro adenomas or macro adenomas. The success rate is around 80% for pituitary micro adenomas secreting ACTH and 50% for pituitary macro adenomas with TSS. The success again depends on the experience of the surgeon. The problem is early or late recurrence of the tumor which happens in 32% of micro adenomas and 50% of macro adenomas. If the recurrent tumor is micro adenoma second surgery can be tried, but the success rate is lower than in the first TSS [20,21].

Medical management of Cushing's disease is considered second-line treatment, usually occurring after surgical failure. It includes the use of a long-acting iSRL like pasireotide and the dopamine agonist cabergoline [20]. Both drugs act on pituitary adenomas to decrease ACTH over secretion.

Other drugs used are the glucocorticoid receptor antagonist mifepristone and adrenal steroidogenesis inhibitors such as ketoconazole/ levoketoconazole and the 11-beta-hydroxylase blockers (such as osilodrostat and metyrapone) [20,22,23].

Glucocorticoid replacement therapy is needed after successful surgery of ACTH-secreting adenomas, until the hypophyseal adrenal axis recovers which might take 1- year or more [20].

The research found that in cases of Cushing disease, adrenally directed medical therapy with ketoconazole normalized urinary free cortisol in 25-50% of patients; with metyrapone, in 43% of patients; and with osilodrostat, in 46% of patients, after 6-8 months of treatment [22,23].

Mifepristone is used in patients with DM and CD and can lower HbA1C [20].

Combination therapy with ketoconazole and metyrapone was very effective against Cushing disease and in one study normalized urinary-free cortisol in 70-80% of patients. Also, there are trials with Cabergoline- decreases ACTH by acting on pituitary adenoma. It decreases the free cortisol in the urine in patients with Cushing's disease (CD) while used alone in 15-48% of the patients.

When used in combination with ketoconazole it normalized urinary free cortisol in 66% of the patients with CD [24, 25,26]. Pasireotide also decreases the ACTH and cortisol in patients with CD by acting as cabergoline on the pituitary gland.

Nowadays levoketoconazole is used for medical treatment of CD which has less liver side effects than ketoconazole.

Mifepristone is used in patients with DM and can lower HbA1c [27].

If other therapy fails Radiation therapy with gamma knife might be utilized with delayed effect during which the medical therapy can be utilized [28].

Bilateral adrenalectomy can be used extremely rare in persistent or recurrent hypercortisolism or severe disease needing immediate intervention [20]. Usually, the pituitary tumor needs to undergo radiation therapy after the procedure because Nelson syndrome might occur. In this syndrome, ACTH producing pituitary tumors continue to grow and synthesize ACTH. These patients post bilateral adrenalectomy need to be on Glucocorticoid and mineralocorticoid therapy for life.

Thyroid Stimulating hormone (TSH)-secreting adenomas of the hypophyseal area usually are macroadenomas. They can synthesize also prolactin in female patients and GH in male patients. The clinical picture is that of hyperthyroidism.

The main treatment is with TSS.

iSRLs therapy can be used before surgery for faster control of hyperthyroidism which acts on TSH producing pituitary adenomas. iSRLs were reported to normalize free T4 (FT4) in 96% of patients, decrease TSH by more than 50% in over 90% of patients, and shrink TSH-secreting adenomas by 46% of the patients. It was also found that approximately 4% of patients required methimazole or propylthiouracil (PTU) which act peripherally on the thyroid gland, in addition to iSRLs, to control their hyperthyroidism before surgery.

Some patients with microadenomas secreting excess TSH might want to avoid surgery and be treated with iSRLs and usually stereotactic radiosurgery -gamma knife [ 29].

Gonadotropin-secreting pituitary adenomas are typically asymptomatic and are treated similarly to nonfunctioning adenomas because they either do not secrete functional gonadotropins or do not secrete enough FSH or LH to produce a clinical syndrome.

Non-secreting pituitary micro adenomas are usually detected incidentally (incidentalomas). They rarely grow to produce mass effect or cause visual field defect. They are best observed. Observational studies showed that enlargement of non-secreting pituitary micro adenomas occurred in 10% of patients, whereas size reduction occurred in 6% of individuals, and remain unchanged in 83% of the patients [30,31]. Usually, it is recommended that non-secreting pituitary micro adenomas be followed with MRI of the hypophyseal area at 1, 3, and 5 years. If the tumor does not change, no further studies are needed. If there is tumor growth or the occurrence of abnormal visual fields (which is extremely rare with nonfunctioning pituitary micro adenomas), then TSS is recommended.

Non-secreting pituitary macro adenomas if they do not cause mass effect, visual field defect or pituitary hypofunction are followed with MRI of the hypophyseal area at 6 months, 1 year, 3 years, and 5 years. If growth, hormonal hypofunction, or visual field defects occur surgery should be considered. Usually left alone without surgery 23% of pituitary non-secreting macro adenomas enlarged, 12% decrease in size and in 65% of the patients they do not change.

If post TSS of non-secreting pituitary micro-adenomas there is no visible tumor and stereotactic radiosurgery (RT) is used regrowth of the pituitary non-secreting micro adenoma happens in 7 % of the cases and without RT in 14%.

If there is a visible tumor after TSS of pituitary macro adenomas and RT are used regrowth happens in 11% of the tumors and without RT in 50% of the tumors meaning that if there is a visible tumor after TSS of pituitary non-secreting macro adenomas stereotactic radiosurgery should be used [30,31].

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### 3. Discussion

The pituitary adenomas arise from the anterior pituitary gland. The anterior pituitary gland arises from the Rathke pouch. The pituitary adenomas form from anterior pituitary cells and are 5 types. The pluripotent pituitary stem cell under the influence of the transcription factors forms the anterior pituitary cells from which the pituitary adenomas arise. The incidence of pituitary adenomas is at least 10% to 38% based on MRI and post-mortem studies. They are micro adenomas – less than 1 cm and macro adenomas- larger than 1 cm. The usual treatment of hyperfunctioning pituitary adenomas or those that cause mass or visual field defect or hypofunction of the remaining pituitary cells is transphenoidal surgery. The only exceptions are the prolactinomas which are treated usually with dopamine agonists first or observation. The success of the surgery depends on the surgical experience. The experienced surgeons perform 3-5 pituitary surgeries per week. Medical treatment and radiation therapy with the exception of prolactinomas are usually done if the surgery is not successful. The surgery of micro adenomas is usually highly successful in experienced hands – 80-90% success-cure in the majority of pituitary micro adenomas. The surgical treatment of pituitary macro adenomas is less apparent- around 50-60%. If there is micro adenoma remaining after the first TSS usually second surgery is needed or radiation therapy with or without medical therapy is used. Sometimes like in acromegaly the surgical debulking can be done before the medical therapy. The big problem with patients with Cushing's disease is the high rates of recurrence of the pituitary adenoma after successful surgery. The prolactinomas are treated usually with dopamine agonists or observation depending on the scenario discussed above. Other modalities of treatment of micro prolactinomas are rarely used as discussed. The non-secreting pituitary tumors depending on the symptoms which they cause, pituitary hypofunction associated with them and size might be observed or treated with surgery with or without radiation therapy.

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#### 4. Conclusion

We wrote a short review about the pathogenesis, incidence, and treatment of pituitary adenomas. Although the misconception is that they are rare tumors, pituitary adenomas occur in at least 10% of the population. We discussed different treatment strategies based on the type of pituitary adenomas.

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#### Compliance with ethical standards

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