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Clinically non-functioning pituitary adenoma

Craig A. Jaffe

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Abstract Non-functioning pituitary tumors are relatively common. A large number of these tumors are incidentally found pituitary microadenomas (< 1 cm) and are usually of no clinical importance. Those tumors that require treatment are generally macroadenomas and come to medical attention because of mass effect and/or hypopituitarism. Visual field defects are present in roughly 70% of patients with non-functioning macroadenoma at the time of diagnosis and the majority of these patients have at least growth deficiency and hypogonadism. By immunocytochemistry, the large majority of these tumors are glycoprotein producing and less commonly they are non-functioning somatotroph, lactotroph or corticotoph adenomas. In contrast to the immunocytochemistry results, only a minority of these tumors actively secrete intact gonadotrophs or glycoprotein subunits. Therapy is directed at eliminating mass effect and correcting hypopituitarism. There are anecdotal reports of tumor shrinkage during therapy with either dopamine agonists or somatostatin agonists; however tumor response to medical treatment is not reliable. For most patients, transphenoidal resection of the tumor is the preferable primary treatment. Surgery improves visual defects in the majority of patients and a lesser number will recover pituitary function. In the past, pituitary radiation was commonly administered following pituitary surgery; however the need for routine radiation has recently been reevaluated. Although tumor recurrence at 10 years post surgery may be as high as 50%, few patients with recurrence will have clinical symptoms. Close follow-up with surveillance pituitary scans should be performed after surgery and radiation therapy reserved for patients having significant tumor recurrence.

Keywords Pituitary · Adenoma · Hypopituitarism · Gonadotroph · Null cell · Radiation therapy · Surgery · Guidelines

C. A. Jaffe (✉)
The University of Michigan, Division of Metabolism, Endocrinology and Diabetes,
Michigan, USA
e-mail: cjaffe@med.umich.edu

Demographics and clinical presentation

Although most patients presenting with pituitary macroadenoma have clinical findings that reflect pituitary hormone hypersecretion, roughly 30% of patients do not have a clinical syndrome of hormone excess. In these patients, pituitary tumors are defined as clinically non-functioning. Whereas some of these tumors neither secrete nor produce pituitary peptides, there is marked heterogeneity in hormone production by apparently non-functioning pituitary tumors. As will be discussed below, careful study of pituitary tissue from patients with clinically non-functioning pituitary tumors demonstrates intact hormone or hormone subunits in the many patients.

A special category of non-functioning pituitary tumors includes pituitary incidentalomas. With the advent and widespread use of MRI and CT, 4–20% of normal individuals are found to harbor a pituitary microadenoma (<10 mm) [1]. This incidence is similar to the reported 10–20% of incidental microadenomas found in autopsy series [3]. As with macroadenoma, some of these tumors produce intact or partial pituitary peptide hormones. However, most of these tumors either do not secrete hormone or secrete hormones at such a low level that clinical syndromes of hormone excess do not develop. The ubiquitous nature of these tumors and the relative low incidence of patients having either macroadenoma or syndromes of pituitary hormone hypersecretion,

suggests that (1) most of these tumors are non-secretory and (2) the large majority of tumors will not appreciably increase in size [1, 7].

As mentioned above, heterogeneity in cell type in non-functioning pituitary tumors is large. Classification of cell type can be accomplished by a variety of molecular, immunological and immunohistocytochemical methods [3, 9, 10]. In vitro investigations have demonstrated that most of these non-functioning tumors synthesize either intact pituitary glycoprotein hormones (FSH, LH, TSH) and/or the free subunits that make up these glycoproteins (α-subunit, β-FSH, β-LH, β-TSH). Less frequently, immunoreactive prolactin, ACTH or GH is found. In less than 30% of non-functioning adenomas, no immunoreactive hormone or hormone subunit is found.

The majority of patients who have clinically-nonfunctioning pituitary adenoma will come to medical attention because of mass effect by a macroadenoma. Lack of a readily diagnosable syndrome of pituitary hormone hypersecretion results in growth of these tumors for many years before discovery of the tumor. This is in sharp contrast to tumors associated hormone hypersecrtion, such as in Cushing's Disease, where the clinical symptoms may be protean and lead to diagnosis of the tumor early on.

The mass effect from pituitary macroadenoma may be manifested by either local pressure effects on non-pituitary tissues or through pituitary compression and subsequent dysfunction. At the time of presentation, roughly 60–70% of patients will have visual-field defects [10, 16], which results from compression of the optic chiasm by the tumor. Patients are frequently unaware of the defect, which only becomes apparent during formal visual-field testing. Headache is frequent. Lateral extension of the tumor into the cavernous sinuses may produce dysfunction of cranial nerves III, IV, V_1, V_2 or VI. Occasionally, non-functioning pituitary tumors can become massive and compress other surrounding brain tissues. These massive tumors may present with a wide variety of symptoms, including temperal lobe seizure, hydrocephalus from compression of the foramen of Monro or the aqueduct of Sylvius, or even symptoms resulting from compression of the brainstem. CSF rhinorrhea may occur if the tumor is locally aggressive and erodes inferiorly into the sella turcica.

In addition to these symptoms, patients may present with signs and symptoms of pituitary insufficiency. GH deficiency and hypogonadism occur in the majority of patients with nonfunctioning macroadenoma. Secondary hypothyroidism and secondary adrenal insufficiency occur in roughly 80 and 60% of these patients respectively.

There are multiple causes for secondary hypogonadism. Hypogonadotropic hypogonadism may be the result of direct compressive effects by a large adenoma. In addition, pituitary stalk compression with subsequent prolactin elevation is a frequent cause of hypogonadism. Modest serum prolactin elevations (generally < 200 ng/ml) occur in the majority of patients and do not necessarily indicate prolactinoma. Of importance, prolactin elevation in patients with prolactinoma correlates well with tumor size. Therefore, modest hyperprolactinemia in the face of a macroadenoma suggests that the tumor is nonfunctional, rather than being a prolactinoma.

Hormonal abnormalities, again most commonly hypogonadism, can result from hypersecretion of either pituitary glycoprotein peptide hormones or, more commonly, their monomeric subunits [9, 10]. In roughly one-third of patients, β-FSH is elevated at baseline. In approximately one-fifth of patients, α-subunit is elevated. FSH hypersecretion occurs less frequently. Rarely, LH hypersecretion may result in abnormally high testosterone levels. Hypersecretion of more than one monomeric subunit with or without LH/FSH is common.

Diagnosis

General

The correct identification of a pituitary mass being a nonfunctional adenoma can be difficult. Without a clinical syndrome of hormone excess, the differential diagnosis of an intrasellar mass is long and includes rest cell tumors (craniopharyngioma, Rathke's cleft cyst, chordoma and others), gliomas, meningioma, germ cell tumors, granulomatous diseases, metastatic tumors and other lesions in addition to pituitary adenoma. In addition, it is not uncommon that a patient presenting with an "incidentally" found pituitary mass and no clear-cut symptoms of pituitary hormone hypersecretion, will in fact have a functioning pituitary tumor. For example, patients having "subclinical" Cushing's Syndrome have been well described. Similarly, with the wide availability of serum insulin-like growth factor I measurements, correct assignment of a pituitary tumor as GH-secreting, rather than non-functioning, is not uncommon.

Biochemical

As described above, some non-functioning pituitary tumors hypersecrete glycoproteins and/or glycoprotein hormone subunits. Elevation in baseline α-subunit, β-FSH, β-LH, FSH or LH can be used to differentiate a pituitary adenoma from other intrapituitary lesions. Because gonadotropins and free subunits are elevated in patients with primary gonadal failure and in postmenopausal women, interpretation of these baseline data must be completed in the context of the patient's gonadal hormone status.

Although measurement of baseline glycoprotein or subunit elevation can be very useful if the levels are elevated,

this occurs in only a minority of patients. Acute administration of intravenous thyrotropin-releasing hormone (TRH) can help differentiate pituitary adenoma from other lesions [5, 10]. This test makes use of paradoxical increases in serum concentrations of gonadotropins and/or free α/β subunit following intravenous TRH. Approximately 40% of patients with non-functioning pituitary adenoma have a positive response to TRH administration. A positive response to TRH is helpful in establishing that a pituitary mass in a hypogonadal patient is a glycoprotein secreting adenoma. Unfortunately, at the present time, TRH is not available for clinical use in the United States.

Radiological

A high quality imaging study is important in the evaluation of a patient suspected of having a pituitary tumor. In general, a MRI performed without and with gadolinium contrast offers the best resolution. If a MRI scanner is not available or if a patient can not be placed in a MRI scanner, high quality CT scanning before and after intravenous contrast can be used.

Treatment

Medical

In contrast to the effectiveness of medical treatment for prolactinomas and some somatotropinomas, medical treatment of non-functioning pituitary tumors is generally ineffective [2, 12, 15]. Non-functioning pituitary tumors frequently have dopamine receptors; however tumors infrequently shrink during administration of bromocriptine or cabergoline. Similarly, these tumors may contain somatostatin receptors. However, tumor visualization on octreotide scans does not correlate with a positive response to octreotide treatment and tumor shrinkage during octreotide therapy is uncommon. Based on these considerations, medical therapy for nonfunctioning adenoma is generally not recommended.

Surgical

The primary treatment for non-functioning pituitary tumors requiring therapy is surgery. Surgical morbidity and cure rate are highly dependent on the experience of the pituitary surgeon [13]. Therefore, an important caveat is that pituitary surgery should be performed by a surgeon who has extensive experience with pituitary surgery and who performs this surgery frequently. The preferred surgery is a transphenoidal approach, which has low associated morbidity and mortality. However, because many of these tumors have extrasellar extensions, craniotomy may be required.

Surgery is highly effective in improving morbidities associated with mass effect by non-functioning pituitary adenoma [4, 6, 16]. The majority of patients with large, nonfunctioning tumors has visual field disturbances at the time of diagnosis, either as a presenting complaint or documented by formal visual field testing. Following surgery, visual deficits improve in 60–88% of patients with normalization in 30–50%. Visual fields have been reported to worsen in 4–11% of patients. Several series have reported relief from headache in over 90% of patients treated by surgery.

Surgery restores endocrine function in a significant number of patients [4, 16, 17]. Depending on the series, the most common pre-operative deficit is either GH or gonadotropin deficiency and in some series, more than 90% of patients have at least one pituitary hormone deficiency prior to surgery. Following surgery, rates of recovery of lost pituitary function have been quite variable, with reports ranging from 16–60%. In general, recovery of the thyroid and adrenal axes are most likely. Recovery of GH secretion has been reported to be as low as 0%. Preservation of some normal pituitary function preoperatively, as demonstrated by elevated prolactin, gonadotropin response to GnRH, or TSH response to TRH predicts a favorable hormonal recovery after surgery. Pituitary function is also more likely to be recovered if the tumor is less than 2.5 cm. Transphenoidal as opposed to a cranial approach is associated with a higher likelihood of preserved or improved endocrine function. Likely, this is at least partially because the transcranial approach is only used for larger tumors, especially for those tumor with suprasellar extension.

The cure rate following surgery is difficult to determine. The majority of microadenomas can be resected completely. In contrast, a large percentage of non-functioning macroadenomas have extrasellar extension so that complete resection of the tumor is impossible without evoking unacceptable risks. In early studies, the radiological recurrence rate at 10 years was reported to be 70–90%. This observation, coupled with a decrease in demonstrable recurrence to roughly 10–20% if post-operative radiation was given, led to the general use of post-operative radiation. It should be noted that the large majority of patients having radiographic evidence for tumor recurrence are asymptomatic. With improved surgical techniques, the recurrence rate at 10 years in patients who have either no or minimal residual tumor after resection and who are not treated with adjuvant radiation has recently been reported to be approximately 50% [16] and perhaps as low as 20% [6].

Unfortunately, there is not a test to accurately determine the risk of post-operative tumor recurrence. Higher tumor invasiveness has generally been associated with increase risk of recurrence, although lack of invasiveness does not guarantee recurrence. Other clinical parameters and proliferative

indices of pituitary cells, such as measurement of Ki-67 antigen, are of unclear significance in predicting recurrence.

Radiation

The case for radiation therapy following surgical resection is reviewed above. In the last few years, whether radiation is needed for all patients has been questioned [6, 11, 14]. Although most patients with non-functioning macroadenoma will have demonstrable recurrence following surgery alone, few of these patients will have clinically important symptoms attributable to the recurrent tumor. If appropriately administered, local complications of radiation treatment alone, which include damage to the optic chiasm or other central structures, are rare. Yet, radiation therapy is not totally benign. Besides causing further hypopituitarism, treatment increases the risk of a second intracranial malignancy, can cause vasculopathy, and might have negative effects on cognition. These considerations have led many experts to withhold radiation after surgery until there is demonstration of significant tumor recurrence and recurrent tumor treated by this approach appears to either stabilize or regress [14]. Whether stereotactic radiosurgery (gamma knife and others) offers any real advantages over conventional external beam fractionated radiotherapy is not known.

Treatment algorithm

In the evaluation of a patient with an apparently non-functioning pituitary tumor, the initial steps include verifying that the intrasellar mass is in fact a nonsecretory adenoma. The differential diagnosis for sellar masses is long and reviewed above. Careful imaging studies, preferably by MRI and interpreted by a qualified neuroradiologist will assist in establishing the origin of the mass. Baseline, formal visual field testing by an ophthalmologist should be performed. Because of the possibility that the patient could have a clinically silent secretory pituitary adenoma, screening tests for acromegaly and Cushing's Syndrome (serum IGF-I and 1 mg dexamethasone suppression test) should be performed. Serum prolactin should be measured. Modest elevations in serum prolactin do not necessarily mean that the tumor is a prolactinoma, whereas moderately elevated or normal serum prolactin can occur because of the "hook-effect" in patients having large macroprolactinomas and massive hyperprolactinemia. Elevation in baseline gonadotropins and gonadotropin subunits suggests that the pituitary mass is a glycoprotein secreting tumor, but increases can be seen with primary hypogonadism. Paradoxical rise in gonadotropin or free subunits in response to TRH occurs in many patients with glycoprotein secreting pituitary adenoma and can be used to confirm that the sellar mass is, in fact, a pituitary tumor.

Pituitary tumor size is used as an important determinant of whether tumors should be surgically resected [8]. Because microadenomas (<1 cm) tend to remain small, conservative management is appropriate for such patients with yearly surveillance imaging studies to insure that the tumor is not enlarging. The frequency of re-imaging the tumor can decrease as clinically indicated over time. Pituitary endocrine function can be disrupted by small, nonsecretory tumors, although hyperprolactinemia, with or without hypogonadotropic hypogonadism is frequently the only demonstrable abnormality.

The surgical management of macroadenomas (>1 cm) is guided by the greater likelihood that these tumors will increase in size over time and the mass effects accompanying the tumor. The initial goals of therapy in this case are to resolve any mass effect and to restore normal endocrine function. The inability of medical treatment to shrink most tumors and the slow nature of radiation treatment leaves pituitary surgery as the best therapy for most patients who have signs or symptoms of mass effect.

If there is no mass effect, conservative therapy may be considered as not all macroadenomas will increase in size over time. This approach is most appropriate for patients who are reliable, very elderly and/or at high surgical risk. Conservative management is also reasonable for more modest sized macroadenoma in young, asymptomatic adults, in whom there is concern that surgery could disrupt the pituitary regulation of reproductive function. In these cases, dedicated follow-up scans of the pituitary should be performed after 3, 6 and 12 months and then yearly with decreasing frequency as dictated by tumor size changes during longitudinal follow-up.

During longitudinal care, if there is evidence for significant tumor growth, pituitary surgery is generally performed. If the patient is not a viable candidate for surgery, pituitary irradiation should be considered. This usually prevents further growth of the tumor. In this subgroup of patients, medical treatment with cabergoline (or bromocriptine) and/or octreotide may also be considered, recognizing that few patients will have a significant response. In addition, the long-term efficacy of medical treatment in the few patients who respond is unknown, necessitating close surveillance.

Most patients with large, non-functioning pituitary adenoma should undergo pituitary surgery. Follow-up imaging studies are generally done 6 and 12 months after surgery and subsequently yearly. Demonstrable tumor remnants after surgery are frequent. Whether all such patients should receive post-surgical radiation has recently been re-evaluated. The lack of progression of remnant size and low incidence of clinical symptoms in operated but not radiated patients coupled with the deleterious effects of radiation suggests radiation can be safely deferred in patients with complete or near-complete resections. Radiation should be administered

if there is a large amount of residual tumor post surgery, especially if the adenoma is clinically aggressive. If radiation is deferred, close observation with high-resolution imaging should be done periodically and radiation administered if there is evidence for recurrence.

Reference

1. Aron DC, Howlett TA (2000) Pituitary incidentalomas. Endocrinol Metab Clin North Am 29:205–221
2. Bevan JS, Webster J, Burke CW, Scanlon MF (1992) Dopamine agonists and pituitary tumor shrinkage. Endocr Rev 13:220–240
3. Buurman H, Saeger W (2006) Subclinical adenomas in postmortem pituitaries: classification and correlations to clinical data. Eur J Endocrinol 154:753–758
4. Colao A, Cerbone G, Cappabianca P, Ferone D, Alfieri A, Di Salle F, Faggiano A, Merola B, de Divitiis E, Lombardi G (1998) Effect of surgery and radiotherapy on visual and endocrine function in nonfunctioning pituitary adenomas. J Endocrinol Invest 21:284–290
5. Daneshdoost L, Gennarelli TA, Bashey HM, Savino PJ, Sergott RC, Bosley TM, Snyder PJ (1993) Identification of gonadotroph adenomas in men with clinically nonfunctioning adenomas by the luteinizing hormone beta subunit response to thyrotropin-releasing hormone. J Clin Endocrinol Metab 77:1352–1355
6. Dekkers OM, Pereira AM, Roelfsema F, Voormolen JH, Neelis KJ, Schroijen MA, Smit JW, Romijn JA (2006) Observation alone after transsphenoidal surgery for nonfunctioning pituitary macroadenoma. J Clin Endocrinol Metab 91:1796–1801
7. Donovan LE, Corenblum B (1995) The natural history of the pituitary incidentaloma. Arch Intern Med 155:181–183
8. Greenman Y, Ouaknine G, Veshchev I, Reider G II, Segev Y, Stern N (2003) Postoperative surveillance of clinically nonfunctioning pituitary macroadenomas: markers of tumour quiescence and regrowth. Clin Endocrinol (Oxf) 58:763–769
9. Harris PE (1998) Biochemical markers for clinically nonfunctioning pituitary tumours. Clin Endocrinol (Oxf) 49:163–164
10. Katznelson L, Klibanski A (1996) Endocrine-inactive, FSH, LH and α-subunit adenomas: clinical findings and endocrinology. In: Landolt AM, Vance ML, Reilly PL (eds). Pituitary adenomas. Churchill Livingstone, New York, pp 127–138
11. Lillehei KO, Kirschman DL, Kleinschmidt-DeMasters BK, Ridgway EC (1998) Reassessment of the role of radiation therapy in the treatment of endocrine-inactive pituitary macroadenomas. Neurosurgery 43:432–438 discussion 438–439
12. Lohmann T, Trantakis C, Biesold M, Prothmann S, Guenzel S, Schober R, Paschke R (2001) Minor tumour shrinkage in nonfunctioning pituitary adenomas by long-term treatment with the dopamine agonist cabergoline. Pituitary 4:173–178
13. Mortini P, Losa M, Barzaghi R, Boari N, Giovanelli M (2005) Results of transsphenoidal surgery in a large series of patients with pituitary adenoma. Neurosurgery 56:1222–1233
14. Park P, Chandler WF, Barkan AL, Orrego JJ, Cowan JA, Griffith KA, Tsien C (2004) The role of radiation therapy after surgical resection of nonfunctional pituitary macroadenomas. Neurosurgery 55:100–106 discussion 106–107
15. Shomali ME, Katznelson L (1999) Medical therapy for gonadotroph and thyrotroph tumors. Endocrinol Metab Clin North Am 28:223–240, viii
16. Snyder PJ (1985) Gonadotroph cell adenomas of the pituitary. Endocr Rev 6:552–563
17. Webb SM, Rigla M, Wagner A, Oliver B, Bartumeus F (1999) Recovery of hypopituitarism after neurosurgical treatment of pituitary adenomas. J Clin Endocrinol Metab 84:3696–3700