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Etiology of Thickened Pituitary Stalks

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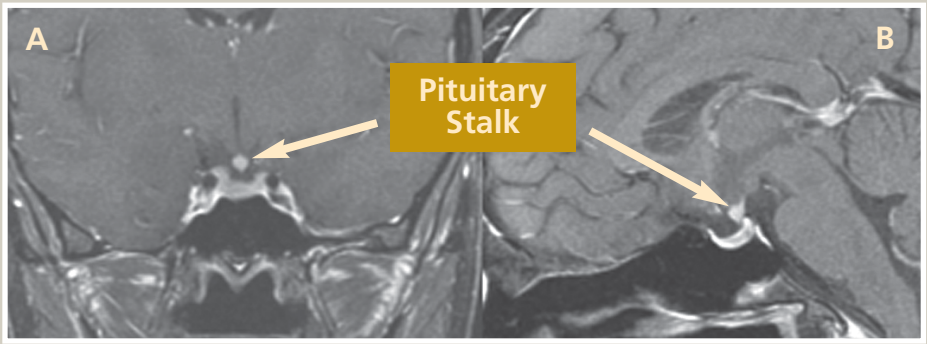
On magnetic resonance imaging, some patients with clinical neuroendocrine disorders have thickened pituitary stalks, the anatomical structure which connects the hypothalamus to the pituitary (Figure 1). These disorders can be classified as neoplastic, inflammatory, or infectious in origin, although there are rare forms of congenital malformations that may give a similar clinical and imaging presentation. Here we will briefly review the diagnostic aspects of the common causes of suprasellar masses that cause thickened pituitary stalks (Table 1). We will not discuss congenital pituitary stalk anomalies, infections involving the pituitary stalk, rare stalk tumors such as pituicytomas, or pituitary adenomas which may extend superiorly.

Figure 1



Example of thickened pituitary stalk A) coronal T1 post-gadolinium B) Sagittal T1 post-gadolinium

Stalk Neoplasms

Neoplasms of the stalk may be primary (i.e., arise from within the central nervous system), or secondary (i.e., spread from sites outside the CNS).

Primary Tumors

Craniopharyngioma

Craniopharyngioma is a tumor that occurs predominantly in childhood but has a second peak incidence in later life. While craniopharyngiomas occur anywhere from the sella to the third ventricle, they are commonly located in the suprasellar location and may extend inferiorly into the sella or from the suprasellar region to both the sella and third ventricle (1-2). In a series of childhood craniopharyngiomas reported by Tomita et al. (2), 96% had calcifications and 93% had cyst formation on MRI. In a series of 21 cases of craniopharyngiomas with mean age of 35 years reported by Shin et al. (1), calcification was detected in 87% and cysts were seen in 91% (38% cysts alone and 43% mixed solid and cystic). Although it is difficult to definitively confirm the diagnosis on imaging, there are features that help differentiate craniopharyngiomas from the other sellar region cystic lesions, i.e., Rathke's cleft cysts and arachnoid cysts. Calcification and the presence of a solid component are both more common in craniopharyngiomas. Shin found that only 13% of Rathke's cleft cysts and 0% of arachnoid cysts had calcifications (1, 3). Shin et al. also found that all of the Rathke's cleft cysts and arachnoid cysts typically had an intrasellar component, whereas craniopharyngiomas were predominantly suprasellar. Some authors report that occasional Rathke's cleft cysts clinically behave like craniopharyngiomas and that they may exist in a spectrum from the benign to the aggressive with some degree of overlap (4).

As with most parasellar masses, craniopharyngiomas usually present with headache, visual disturbance and/or endocrine dysfunction. Surgery and external beam radiotherapy are the most commonly used therapies (2, 5). The extent of surgical resection is controversial because of the risks associated with surgery in this location.

Germ Cell Tumors

Germ cell tumors rarely present in the suprasellar region and may synchronously occur in the pineal region. They usually occur in children and young adults. Diabetes insipidus is common. MRI

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typically shows homogeneous or heterogeneous enhancement in the suprasellar region which often extends into the hypothalamus (6). Unlike craniopharyngiomas, they are usually not cystic. Although the serum and CSF may have elevated levels of alpha-fetoprotein (AFP) and/or beta-human chorionic gonadotrophin (beta-HCG) in non-germinomatous germ cell tumors, most pure germinomas do not elevate AFP or beta-HCG. They are sensitive to chemotherapy and radiation therapy with reports of 90% cure rate of pure germinomas (7).

Secondary Tumors

Metastases

When metastases from systemic cancer spread to the pituitary and its stalk, patients typically present with diabetes insipidus, a differentiating feature from pituitary adenomas. The diagnosis is usually made on the basis of the clinical history, evidence of known metastatic disease, imaging and, when necessary, CSF cytology.

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH), a rare multi-system disease which typically occurs in children, is caused by a monoclonal expansion of dendritic cells that typically involves bones, skin and lungs. When the hypothalamus and pituitary are involved central diabetes inspidus (DI) is frequent (8).

Makras and colleagues (9) have reported the anterior and posterior pituitary gland function and MRI findings in 17 adults with multisystem LCH. Of these, 14 (82%) had abnormal hypothalamic-pituitary imaging. Lack of the normal posterior pituitary lobe bright spot was found in all patients with diabetes insipidus; infundibular enlargement was found in 47%; pituitary infiltration in 35% and hypothalamic infiltration in 18%. Diabetes insipidus was found in 94% and anterior pituitary dysfunction in 59%. In the series of pediatric central DI, 5 of 12 patients with LCH-induced central DI had thickened pituitary stalks (10).

The imaging of LCH can mimic that of germinoma and other diseases. Prosch and colleagues (8) report a case in which a thickened pituitary stalk suggested Langherhans cell histiocytosis, which later was found to be a germinoma. Diagnosis is established by biopsy, usually of a bone lesion, lymph node or skin.

Table 1

Major Causes of Thickened Stalk

- Inflammatory
  - Lymphocytic Hypophysitis / Infundibulitis
  - Sarcoidosis
- Neoplastic
  - Craniopharyngioma
  - Germ cell tumor
  - Metastases (including lymphoma)
  - Pituitary adenomas
  - Other primary CNS tumors
- Langerhans cell histiocytosis (uncertain classification)
- Infection
- Congenital anomalies

Hypophysitis due to Inflammatory Lesions

Lymphocytic Hypophysitis

Lymphocytic hypophysitis (LH) usually presents in the peripartum period with hypopituitarism and symptoms of a mass lesion in the sella and/or suprasellar region. LH may be subdivided into inflammation of the adenohypophysis (LAH) or, less commonly, lymphocytic infundibuloneurohypophysitis (LINH) which clinically presents as diabetes insipidus. LH is a rare disorder; Caturegli et al. reported a prevalence of 8 cases in 905 surgical pituitary specimens (0.88%) from 1986 to 2004 at Johns Hopkins Hospital (11). It is suspected to be an autoimmune disease.

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LH typically presents as a sellar mass, anterior pituitary dysfunction, diabetes insipidus and/or hyperprolactinemia in a young pregnant or postpartum woman (11-14). Imaging features that may suggest a preoperative diagnosis of LH include symmetric enlargement of the gland with diffuse contrast enhancement extending into the stalk and basal hypothalamus in a tongue-like fashion without erosion of the sella floor. In contrast, pituitary macroadenomas commonly are asymmetric masses that may erode the sella floor and displace the stalk (11-12, 15-18). LINH may reveal normal anterior pituitary imaging with an abnormally enhanced and thickened stalk and absence of the normal posterior gland hyperintensity (19).

LINH was reported by Imura et al. (19) in 17 patients with idiopathic diabetes insipidus of a few months to several years duration. Biopsy of two cases revealed infiltration, primarily with lymphocytes and plasma cells. None of the patients in this series developed clinical symptoms or signs of hypopituitarism or hypothalamic dysfunction other than diabetes insipidus; however, several had impaired secretory responses of GH to insulin-induced hypoglycemia (19). On MRI, thickening of the stalk was seen only in the patients who had diabetes insipidus for less than two years duration, with the abnormalities disappearing during follow-up.

Maghnie et al. (20) have reported circulating vasopressin-cell auto-antibodies in 75% of 20 young patients with idiopathic central diabetes insipidus (CDI). However, these autoantibodies were also found in patients with central DI due to Langerhan's cell histiocytosis and germinoma, indicating that vasopressin-cell auto-antibodies cannot be considered completely reliable markers of autoimmune central DI. Accordingly, a biopsy is required in order to confirm the diagnosis definitively at the time of presentation. Central DI may also be the early sign of an evolving process necessitating rigorous clinical and neuroradiologic follow-up to rule out neoplasms, LCH, or other etiologies (21).

Hypothalamic-Pituitary Sarcoidosis

Sarcoidosis, a multi-system disease of unknown etiology, is characterized by non-caseating granulomas which may involve the pituitary stalk leading to enlargement of the stalk on imaging and clinical neuroendocrinological abnormalities. Although sarcoidosis involving the central nervous system has been reported to occur in about 5% of cases, recently hypothalamic-pituitary sarcoidosis was only reported to occur in nine of more than 1600 (< 0.6%) sarcoidosis patients (22). Moreover, all nine of these patients had evidence of sarcoidosis involving multiple sites, with

seven of the nine having four or more affected organs. All of the patients had pulmonary involvement, other neurologic lesions were present in seven and sinonasal sarcoidosis was confirmed in five patients.

When the hypothalamic-pituitary axis is involved, patients generally present with symptoms of hypopituitarism. Diabetes insipidus has been the most commonly reported manifestation although hypogonadism, manifested as decreased libido or amenorrhea, was the most common clinical presentation in the recent series cited above (22). The MRI appearance of hypothalamic-pituitary involvement typically includes thickening of the stalk, lesions in the floor of the third ventricle, and abnormal enhancement. There may also be enhancement of the leptomeninges and parenchymal brain lesions.

The cerebrospinal fluid may show nonspecific abnormalities and serum and CSF angiotensin converting enzyme elevations may occur, but are often normal (23). Glucocorticoids are the mainstay of therapy. In cases unresponsive to corticosteroids or when steroid-sparing regimens are preferred, azathioprine, methotrexate, chloroquine and infliximab have been used (23-26). Abnormal enhancement on imaging usually regresses with therapy but may recur with steroid tapering. Hormone deficiencies generally persist despite imaging improvements (22).

In summary, the leading causes of thickening of the pituitary stalk are neoplastic and inflammatory diseases. A search for systemic diseases that can involve the hypothalamic-pituitary axis is usually undertaken; if these are not found consideration of primary neoplasms or autoimmune hypophysitis become leading considerations.

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Pituitary Apoplexy

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Pituitary apoplexy (apoplexy - to disable by a stroke) is a clinical syndrome characterized by the abrupt onset of characteristic signs and symptoms, most commonly headache, nausea, visual disturbance, and ophthalmoplegia, in association with hemorrhage or infarction within the pituitary fossa.

Epidemiology of pituitary apoplexy

Most of what is known about the frequency of pituitary apoplexy comes from series of patients treated operatively for pituitary tumors. These studies suggest apoplexy is not rare, with 5% of patients presenting with classical apoplexy (1-6). Almost all apoplexy cases arise in the setting of a pre-existing pituitary tumor, but in more than 80% of cases the tumor has not been previously diagnosed (4, 7-11).

Surgical series of pituitary adenomas and apoplexy may be biased to include patients with larger or more symptomatic tumors, but apoplexy is not uncommon in true incidentalomas. In a prospective study of pituitary adenomas found incidentally by magnetic resonance imaging (MRI), 10% developed classically symptomatic pituitary apoplexy during five years of follow-up (12). The tumors in which apoplexy occurred ranged in size from 18-24 mm prior to the hemorrhagic event.

Pituitary apoplexy appears to be most common in clinically non-functioning tumors, with only 32% of tumors staining for prolactin, growth hormone, or adrenocorticotrophic hormone (approximately 10% each), and 1% of tumors staining for more than one hormone (1, 2, 4, 5, 7, 9-11). Pituitary apoplexy is slightly more common in males (60% of cases) than females. The mean age of onset of apoplexy is 50 years, but the ages at diagnosis ranged from 15-90 years of age.

Most episodes of apoplexy occur in macroadenomas. Autopsy series have found macroadenomas in 0.03% (13) and a population-based MRI imaging study found lesions consistent with macroadenomas in 0.16% (14). Therefore, one out of 1,000 individuals in the population may be at risk for pituitary apoplexy.

The clinical syndrome of pituitary apoplexy

As a result of the anatomy of the pituitary region (Figure 1), an expanding mass can impinge on the optic chiasm of cranial nerve II superiorly, or cranial nerves III, IV, V (ophthalmic and maxillary divisions), and VI as they pass through the cavernous sinus lateral to the sella. The most common symptoms are sudden headache in 89% and nausea/vomiting in 57%. More than 50% of patients complain of visual disturbance; photophobia (40%) or facial pain or numbness (7%) are less common. The most common signs include decreased visual acuity in 56%, diminishment of visual fields in 28%, and ophthalmoplegia in 46% of patients (1-11). Cranial nerve III (oculomoter nerve) is most commonly affected, with signs including ptosis, mydriasis, lack of pupillary light and/or accommodation reflex, and/or deviation of the affected eye downward and laterally in 51% of patients (2, 4, 9, 10). Cranial nerve VI (abducens) defects, including restriction of inward gaze is found in 29%. Cranial nerve IV (trochlear) involvement can cause inward gaze or diplopia in 9% (2, 4, 9, 10).

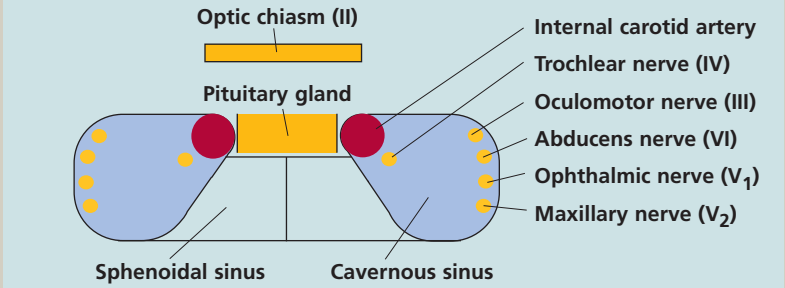
Infarction with attendant edema or hemorrhage within a pituitary tumor frequently results in necrosis of the sellar contents. Central adrenal insufficiency is common (61%) in the acute phase (11), in some cases leading to hypotension or shock if glucocorticoid therapy is not instituted promptly. Transient disorders of sodium homeostasis are common due to the syndrome of inappropriate ADH and diabetes insipidus, but permanent diabetes insipidus occurs in less than 10% (1, 3, 4).

Diagnosis of pituitary apoplexy

The primary challenge in making the diagnosis of pituitary apoplexy is considering the diagnosis, as only 17% of cases arise in a known pituitary tumor (4, 7-11). The presence of visual symptoms or ophthalmoplegia associated with the rapid onset of headache should prompt consideration of pituitary apoplexy, although other "apoplectic" events such as subarachnoid hemorrhage should also be considered. The occurrence of apoplexy during surgery, or in patients who are otherwise unresponsive or uncooperative, can be especially challenging to diagnose.

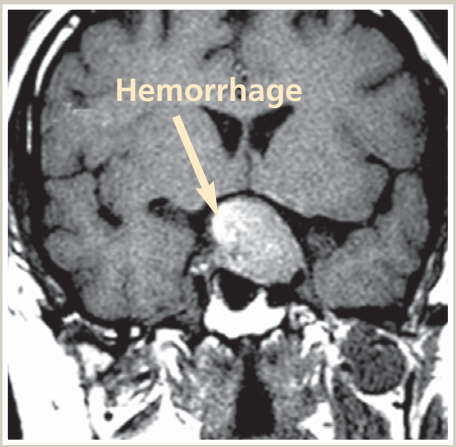
Although pituitary apoplexy is primarily a clinical diagnosis, imaging studies have an important role in the diagnosis. Because the presentation of pituitary apoplexy may suggest the diagnosis of sub-arachnoid hemorrhage or other intracranial hemorrhage, a non-contrast head computed tomography (CT) is often the first study performed. CT does not reliably allow detection of hemorrhage or infarction in pituitary tumors (sensitivity of less than 30%) (2-4, 9-10), but the presence of a mass arising from the pituitary in this setting should prompt evaluation with magnetic resonance imaging (MRI).

Figure 1



Schematic of coronal section through pituitary and adjacent structures

Figure 2



T1 pre-contrast MRI image of acute hemorrhage within a pituitary adenoma

MRI is the study of choice for diagnosis of pituitary apoplexy with a sensitivity of 68-100% for hemorrhage or infarction within the pituitary gland (2-4, 9-10). Hemorrhage is most often seen acutely as high signal intensity on non-contrast T1 weighted images (Figure 2), and infarction as peripheral or inhomogeneous enhancement after administration of gadolinium (15). As necrosis leads to liquefaction, fluid levels may develop and ring enhancement becomes common weeks to months after the event (16-17). In the long term, even patients not operatively managed may develop an empty or partially empty sella as necrotic tissue is remodeled and removed (9, 16, 18).

Stabilization and medical evaluation of patients with pituitary apoplexy Even before the diagnosis is confirmed, any serious consideration of pituitary apoplexy should prompt the immediate administration of high, "stress-dose" glucocorticoid therapy. High dose steroids will prevent the dire consequences of untreated adrenal insufficiency in the setting of a severe physiologic stress and may also improve neurologic deficits via their anti-edema effects. Glucocorticoids should be continued until the diagnosis of pituitary apoplexy can be ruled out. Detection and management of electrolyte abnormalities, primarily disorders of sodium regulation, is the next priority.

Treatment of any other endocrine abnormalities can usually be delayed until a new baseline is reached. Nonetheless, it is useful to document evidence for other endocrine abnormalities at the time of presentation. Diagnosis of a hypersecretion syndrome may influence choice of therapy and provides an important guide to long term monitoring for recurrence. In the setting of acute illness, laboratory evaluation of cortisol hypersecretion is not useful, but measurements of prolactin, free thyroxine, and IGF-I may be helpful if elevated. Documentation of hypersecretion prior to surgery may be the only information on tumor type available after apoplexy because tissue necrosis may prevent immunohistochemical diagnosis (1-2, 4-5, 7, 9-10, 19).

Acute management of pituitary apoplexy Rapid surgical decompression remains the therapy of choice for pituitary apoplexy. The primary rationale for prompt surgical management is the recovery and preservation of neurologic function, with better recovery of vision if surgery is performed within one week after presentation (2, 4). Surgery has led to complete resolution of visual acuity deficits in 100%, normalization of visual fields in 50-75%, and resolution of ocular paresis in 65-73% patients when performed within one week (2, 4). Visual acuity outcomes have been significantly worse when surgery was performed more than one week after the event (complete resolution in 45%), but there is conflicting data on whether early surgery improves visual field recovery (2, 4). Early versus delayed surgery does not appear to affect recovery from ophthalmoplegia, primarily because it tends to resolve regardless of surgical timing.

In most surgical series, at least a small percentage of patients were medically or conservatively managed. In most of these cases, ophthalmoplegia (2, 11, 20) and visual function (20-21) improved without surgical decompression. Whether recovery would have been more complete or more rapid with decompression is unclear, but this observation raises the possibility that some patients might be managed conservatively with good outcome. Three retrospective series including significant proportions of non-surgically managed apoplexy patients have been published, including 108 total patients with apoplexy (9-10, 22). The clinical presentations of apoplexy in these series were similar to those reported in earlier surgical series, and 53% of the patients were managed conservatively. The criteria for surgical management in one series were worsening visual deficits or alterations in consciousness. In the others, these criteria were not explicit, but patients with visual field deficits were more likely to be managed surgically than conservatively (9-10, 22). Visual field defects (excluding blindness) resolved in 45% of surgically managed patients and 79% of conservatively managed patients. Similarly, ophthalmoplegia resolved in 64% of surgical patients and 87% of conservatively managed patients. The superior neurologic outcomes of patients treated conservatively likely reflects the assignment of patients with more severe neurologic compromise to the surgical groups, so these data should not be interpreted to mean that medical management is superior to surgical management in an unselected population. However, these studies do suggest that if patients are appropriately selected and closely monitored, neurologic outcomes can be favorable without surgery.

Based on all of the available evidence, rapid (within one week) surgical decompression is indicated for the majority of patients presenting with pituitary apoplexy. The best candidates for medical management of apoplexy would be those patients with only ocular palsy or mild and non-progressive visual loss that is rapidly reversible with steroid treatment. In practice, the threshold of symptom and sign severity above which surgical management should

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be recommended is likely to depend in part on the availability of an experienced pituitary surgeon. Outcomes after transsphenoidal surgery are better for higher volume centers and surgeons (23). In cases where surgery is mandated by the severity of the presentation, transfer to a high volume center may be beneficial if the patient is sufficiently stable and the transfer can occur quickly.

Intermediate and long term management after pituitary apoplexy Many patients are left with permanent endocrine deficits requiring long-term management after pituitary apoplexy. Up to 90% of patients require replacement of at least one anterior pituitary hormone (1, 8-10, 17, 24-25). In aggregate data from several series, the rate of hypoadrenalism was 74%, hypothyroidism was 70%, and hypogonadism was 67% (2, 4, 7, 9). Conversely, endocrine hypersecretion may persist if a secreting tumor in which apoplexy arose is not completely removed or entirely necrotic, or may recur after a period of remission (10, 26). Finally, tumors may exhibit regrowth after either medical or surgical management of apoplexy (1, 9-10). Therefore, all patients should undergo comprehensive post-apoplexy endocrine evaluation followed by continued endocrine monitoring and periodic imaging.

Conclusions Pituitary apoplexy is a clinical syndrome caused by hemorrhage or infarction within a pre-existing pituitary mass lesion. Prompt diagnosis is important because failure to treat the commonly associated adrenal insufficiency can prove fatal, and early treatment improves neurologic outcome. Most patients require rapid surgical decompression. Although some patients may be treated non-surgically, the criteria for selecting such patients are not well-defined. Hypopituitarism and the possibility of tumor recurrence mandate both long-term endocrinologic and imaging surveillance for all patients recovering from pituitary apoplexy.

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RESEARCH STUDIES AVAILABLE

Patients may qualify for research studies in the Neuroendocrine Clinical Center. We are currently accepting the following categories of patients for screening to determine study eligibility. Depending on the study, subjects may receive free testing, medication and/or stipends.

SUBJECTS	STUDIES	CONTACT 617-726-3870
Newly diagnosed acromegaly	• Evaluating preoperative medical treatments	Karen Pulaski-Liebert, R.N. Dr. Beverly M.K. Biller
Cushing's Syndrome	• Evaluating a potential new medical therapy	Karen Pulaski-Liebert, R.N. Dr. Beverly M.K. Biller
Patients with active acromegaly	• Body composition and cardiovascular evaluation	Dr. Anne Klibanski Dr. Tamara Wexler
Patients with history of cured acromegaly with or without hypopituitarism	• Body composition and cardiovascular evaluation • GH replacement study in patients with GH deficiency	Dr. Anne Klibanski Dr. Tamara Wexler
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Healthy and overweight adolescent girls, ages 12-18	• Investigating body weight in relation to GH and ghrelin secretion in adolescents	Dr. Anne Klibanski Dr. Madhu Misra
Women and adolescent girls with anorexia nervosa	• Investigating effects of rhGH on bone metabolism	Dr. Anne Klibanski Dr. Madhu Misra
Women with anorexia nervosa	• New therapies	Dr. Karen K. Miller Dr. Anne Klibanski
Women and men, ages 18-45	• Investigating body weight and GH secretion • GH treatment in abdominal obesity	Dr. Andrea Utz Dr. Karen K. Miller
Healthy women, ages 18-45	•Investigating the link between cortisol regulation and bone density	Dr. Elizabeth Lawson Dr. Karen K Miller Dr. Anne Klibanski
Women with irregular menstrual periods (hypothalamic amenorrhea), ages 18-45	•Investigating the link between cortisol regulation and bone density	Dr. Elizabeth Lawson Dr. Karen K Miller Dr. Anne Klibanski
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HIV positive men and women with fat redistribution	• Assessment of coronary artery calcification •Lifestyle modification strategies, including exercise and insulin sensitization	Dr. Steven Grinspoon Dr. Janet Lo Katie Fitch, ANP
HIV positive men and women with fat redistribution	• Use of GHRH, a growth hormone secretagogue, to increase endogenous GH levels, improve fat distribution and lipid profile • Among patients with reduced GH response to standard GH secretion testing, use of low dose GH as above	Dr. Steven Grinspoon Janet Lo, M.D. Jim Liebau, ANP

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Mid-May 2008,
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Free admission to patients and family.
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To learn more about acromegaly and advances in surgery, radiation, and medical therapy. Speakers will include specialists in acromegaly and other patients diagnosed with acromegaly.

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Physicians with questions may contact:
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SERVICES AVAILABLE

Facilities The Neuroendocrine Center is located on the 1st floor (Suite 112) of Zero Emerson Place at the Massachusetts General Hospital. A test center is available for complete outpatient diagnostic testing, including ACTH (Cortrosyn) stimulation; Insulin tolerance; CRH stimulation; Oral glucose tolerance and growth hormone stimulation testing. Testing for Cushing's syndrome can also be arranged, including bilateral inferior petrosal sinus ACTH sampling for patients with ACTH-dependent Cushing's syndrome.

Neuroendocrine Clinical Conference A weekly interdisciplinary conference is held to discuss all new patients referred to the Neuroendocrine Center and to review patient management issues. It is a multidisciplinary conference, attended by members of the Neuroendocrine, Neurology, Neurosurgery, Psychiatry and Radiation Oncology services. Physicians are welcome to attend and present cases.

Physicians' Pituitary Information Service Physicians with questions about pituitary disorders ay contact Dr. Biller or Dr. Klibanski at (617) 726-3965 within the Boston area or toll free at (888) 429-6863, or e-mail to pituitary.info@partners.org.

Scheduling Outpatient clinical consultations can be arranged by calling the Neuroendocrine Center Office at (617) 726-7948.

PARTNERS HEALTHCARE
MASSACHUSETTS GENERAL HOSPITAL
A HARVARD MEDICAL SCHOOL TEACHING AFFILIATE

MGH Neuroendocrine Clinical Center Bulletin

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