Acromegaly and Hyperprolactinemia

Series Editors:
Bryan McIver, MB, PhD
Consultant in Endocrinology
Mayo Clinic and Foundation
Rochester, MN

Paul R. Conlin, MD
Assistant Professor of Medicine
Director, Endocrinology Fellowship Program
Harvard Medical School
Boston, MA

Contributor:
Bryan McIver, MB, PhD
Consultant in Endocrinology
Mayo Clinic and Foundation
Rochester, MN

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INTRODUCTION

The pituitary-hypothalamic axis functions as a central regulator of hormone action, interconnecting the central nervous system with most of the major endocrine organs. Diseases of this system are due to overproduction or underproduction of one or more hormones or to the development of an expansile pituitary mass, which causes compression of surrounding structures, most commonly the optic chiasm and hypothalamus.

In most cases, excess pituitary hormone production is caused by the development of a pituitary adenoma, a benign neoplasm that retains almost complete differentiated cell function but that fails to respond normally to pituitary-hypothalamic feedback control mechanisms. An enlarging pituitary mass may compress the remaining normal pituitary tissue, resulting in gradual loss of function of the pituitary hormones secreted by these tissues, which may complicate the diagnosis and management of these diseases. Reduced pituitary function also may occur as a result of a nonfunctioning pituitary mass, most often an adenoma, or because of destruction arising from trauma, infection, inflammation, or infiltration of the pituitary fossa.

At least eight functional hormones are secreted from the pituitary gland, six from the anterior lobe (the adenohypophysis), and two from the posterior lobe (the neurohypophysis). Most of these hormones can cause specific syndromes of oversecretion or undersecretion (Table 1). All of these disorders are rare and the symptoms may be vague and nonspecific, complicating the diagnosis. Pituitary diseases may be among the most challenging of all endocrine diseases to diagnose and treat.

ACROMEGALY

OVERVIEW

Excess secretion of growth hormone (GH) causes two overlapping syndromes: gigantism, which occurs in childhood and adolescence, prior to fusion of the bony epiphyses; and acromegaly, which occurs in adults. In both cases, the condition results from hypersecretion of GH from the adenohypophysis, almost always caused by a pituitary adenoma or, more rarely, by hypersecretion of growth hormone-releasing hormone (GH-RH) from the hypothalamus or elsewhere. The cause of the condition is poorly understood, although there is some evidence that altered hypothalamic control might influence the development of some pituitary adenomas.

Acromegaly is a rare disease, with an estimated annual incidence of approximately 3 cases per million persons and a prevalence of approximately 50 cases per million. Men and women are equally affected. The average age at diagnosis is approximately 40 to 45 years, and there is evidence that an earlier onset is associated with more aggressive tumors. In most cases, however, the clinical features develop slowly and insidiously. Disease presentation often is overshadowed by secondary conditions including diabetes, hypertension, and vascular disease. Because the diagnosis is frequently made late in the disease process, the causative pituitary tumor has the opportunity to grow and by the time of diagnosis is usually a macroadenoma, often extending beyond the pituitary fossa.

High circulating concentrations of GH stimulate hepatic production of insulin-like growth factor 1 (IGF-1; somatomedin C), which mediates virtually all of the end-organ effects of GH. IGF-1 acts on a broad array of organ systems, most prominently connective tissue, skeletal and cardiac muscle, and bone. Prior to closure of the epiphyses in late adolescence, GH stimulates longitudinal growth of the long bones, increasing stature and limb length. Children and adolescents with gigantism can therefore reach unusual height and will continue to grow unless puberty proceeds normally. Interruption of pubertal development is a common consequence of the pituitary compression that accompanies a GH-secreting pituitary macroadenoma. Such interrupted puberty permits longitudinal growth to continue unchecked without medical intervention. In contrast, onset of acromegaly in adulthood does not increase height. However, cortical bone thickness does increase in adult acromegalic patients and, along with thickening of subcutaneous connective tissue, results in the characteristic phenotypic features of acromegaly (Table 2, Figure 1).
Thickening of connective tissue contributes to enlargement of the hands and feet, coarsening of the facial appearance, prognathism (prominence of the lower jaw), and enlargement of the tongue, lips, nose, and ears. Gaps commonly develop between the teeth as the jaw enlarges in long-standing acromegaly. The voice deepens as the larynx enlarges. Snoring and sleep apnea are common as a result of increased connective tissue thickness in the soft palate and nasopharynx.6

Enlargement also is seen in several visceral organs, including the liver, kidneys, heart, and thyroid gland, with a goiter being a frequent finding in acromegaly. Thickening of the skin also is associated with increased sweating, and increased sebum production results in greasy skin and a predisposition to acne. Osteoarthritis affecting the large joints commonly accompanies acromegaly, presumably because of changes in cartilage growth and repair.

A combination of myxedematous changes and increased connective tissue deposition may cause nerve entrapment syndromes, most often carpal tunnel syndrome. Although rare, cranial nerve defects also have been reported.7 Increased muscle bulk is a common accompaniment of acromegaly, but a poorly understood myopathy also is seen, with weakness as a consequence. Weakness may be exacerbated in men by the development of central hypogonadism, the result of pituitary insufficiency.8

Hypertension, premature vascular disease, and metabolic changes including dyslipidemia, insulin resistance, and diabetes are common. Mortality rates are dramatically increased for patients with uncured acromegaly, the result of increased rates of myocardial infarction and stroke. These changes are at least partially reversible with cure of the acromegaly.5

Some patients with acromegaly also develop hypopituitarism as a result of compression of the remaining normal pituitary tissue by the macroadenoma that commonly causes acromegaly. Most frequently, hypopituitarism manifests as hypogonadotropic hypogonadism with arrested puberty in children and adolescents, erectile failure and loss of libido in men, and secondary amenorrhea in women. Visual field defects, in particular bitemporal hemianopsia, occur with enlargement and suprasellar extension of the pituitary adenoma, which results in distortion and compression of the optic chiasm (Figure 2).

Perhaps the oldest description of gigantism and acromegaly occurs in the Bible’s Old Testament story of David and Goliath. The descriptions of Goliath and of the outcome of his battle with David encompass all of the major features of acromegaly and, even today, act as a useful reminder for practicing endocrinologists. Goliath’s physique reflected his tall stature and muscle bulk, and his acromegalic features may have contributed to his ferocious appearance. The onset of his disease in childhood (explaining the tall stature) makes it likely that he suffered from a large pituitary macroadenoma. Almost certainly he was hypogonadal, making it quite likely that he was a “gentle giant” rather than the fierce warrior depicted by the victors. Despite the large muscle bulk caused by acromegaly, he would have been relatively weak and not particularly fast. His bitemporal hemianopsia may have permitted David to approach unseen from the side. The stone from David’s sling probably fractured his osteoporotic skull, as osteoporosis also is a feature of hypogonadism. Finally, Goliath’s panhypopituitarism may have resulted in adrenal insufficiency, making recovery from his injury less likely. The battle was almost certainly one-sided in David’s favor.

### Table 1. Recognized Pituitary Hormones and Associated Syndromes

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Excess</th>
<th>Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anterior lobe hormones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>Cushing’s disease</td>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td>LH / FSH</td>
<td>?Preocious puberty</td>
<td>Hypogonadotropic hypogonadism</td>
</tr>
<tr>
<td>GH</td>
<td>Acromegaly/gigantism</td>
<td>Dwarfism/adult GH deficiency</td>
</tr>
<tr>
<td>TSH</td>
<td>Hyperthyroidism</td>
<td>Central hypothyroidism</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Hyperprolactinemia</td>
<td>Failure of lactation</td>
</tr>
<tr>
<td><strong>Posterior lobe hormones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADH</td>
<td>SIADH</td>
<td>Diabetes insipidus</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>No recognized syndrome</td>
<td>No recognized syndrome</td>
</tr>
</tbody>
</table>

ACTH = adrenocorticotropic hormone; ADH = antidiuretic hormone; FSH = follicle-stimulating hormone; GH = growth hormone; LH = luteinizing hormone; SIADH = syndrome of inappropriate antidiuretic hormone; TSH = thyroid-stimulating hormone.
CASE PRESENTATION
Initial Presentation

A primary care physician refers a 52-year-old woman to an endocrinologist because of difficulty controlling her type 2 diabetes and hypertension.

History

The patient first developed diabetes 4 years ago, with classic symptoms of thirst, polyuria, and fatigue. Her fasting blood glucose level at that time was 320 mg/dL and glycosylated hemoglobin (HbA1c) level was 12.5%. She was advised about her diet and prescribed glipizide in increasing doses over the next year. Because of continued poor glycemic control, metformin was added to the glipizide, but the patient proved intolerant to the new drug even at low doses because of diarrhea. Thus, metformin was stopped and pioglitazone was prescribed. The patient’s fasting blood glucose ranged from 150 to 200 mg/dL with HbA1c persistently above 9.5%. A recommendation was made to commence insulin treatment and the patient was referred for this conversion.

In addition to her diabetes, the patient has a 5-year history of moderately controlled hypertension, with an initial blood pressure of approximately 170/105 mm Hg. Treatment with a diuretic was unsuccessful, and an angiotensin-converting enzyme (ACE) inhibitor was prescribed. Over the last year, the patient’s blood pressure has ranged from 140/80 mm Hg to 160/100 mm Hg. There is no history of vascular disease.

The patient has been otherwise well and is asymptomatic, but she is frustrated with her inability to control her diabetes. On direct questioning, she acknowledges a change in her facial appearance over approximately 10 years, with greater prominence of her nose and

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**Table 2. Features of Pituitary Acromegaly and Gigantism**

<table>
<thead>
<tr>
<th>Pituitary effects</th>
<th>Metabolic effects</th>
<th>Cardiovascular effects</th>
<th>Neoplastic effects</th>
<th>Miscellaneous effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panhypopituitarism</td>
<td>Diabetes mellitus</td>
<td>Altered vascular risk profile</td>
<td>Skin tags (fibrous, benign)</td>
<td>Osteoarthritis of large joints</td>
</tr>
<tr>
<td>Bitemporal hemianopsia</td>
<td>Mixed hyperlipidemia</td>
<td>Ventricular hypertrophy</td>
<td>Adenomatous colon polyps</td>
<td>Hyperhidrosis</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>Hypertension</td>
<td>Atherosclerotic vascular disease</td>
<td>Colonic adenocarcinoma</td>
<td>Acne, greasy skin</td>
</tr>
<tr>
<td>Headaches</td>
<td>Fluid retention</td>
<td></td>
<td></td>
<td>Goiter, diffuse</td>
</tr>
<tr>
<td>Pituitary apoplexy</td>
<td></td>
<td></td>
<td></td>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td>Sleep apnea syndrome</td>
</tr>
</tbody>
</table>

**Growth effects**

Longitudinal growth of long bones (prepubertal only)

Prognathism

Macroglossia

Dental changes

Growth of cartilage (nose, ears)

Enlargement of hands (change of ring size)

Enlargement of feet (change of shoe size, widening of feet)

**Metabolic effects**

Diabetes mellitus

Mixed hyperlipidemia

Hypertension

Fluid retention

**Cardiovascular effects**

Altered vascular risk profile

Ventricular hypertrophy

Atherosclerotic vascular disease

**Neoplastic effects**

Skin tags (fibrous, benign)

Adenomatous colon polyps

Colonic adenocarcinoma

**Miscellaneous effects**

Osteoarthritis of large joints

Hyperhidrosis

Acne, greasy skin

Goiter, diffuse

Carpal tunnel syndrome

Sleep apnea syndrome

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**Figure 1.** An adult with acromegaly, showing the classic phenotypic features. These include prominent supraorbital ridges, enlargement of nose and tongue, and coarsening of the facial features. The hands and feet are large and “spade-like.”
coarsening of her features. Her shoe size has increased two sizes and three widths, and she has had her wedding ring enlarged on two occasions. She acknowledges skin changes of increased acne and greasiness. She also has noticed excessive sweating without heat intolerance, which she has blamed on menopause occurring 5 years earlier. She has not experienced hot flashes.

**Physical Examination**

The patient appears acromegalic (Figure 1), with prominence of the nose, supraorbital ridging, macroglossia, and fullness of the lips. She has a 2-mm gap between her front teeth. Her hands are large, masculine, and “spade-like” with swelling of the digits; her feet are similarly large and puffy. Her stature is normal. There are multiple skin tags over the anterior chest wall. A goiter (approximately 35 g) is noted without focal nodularity. She is hypertensive with a blood pressure of 154/98 mm Hg, and a fourth heart sound is noted. There is evidence of early diabetic retinopathy with scattered microaneurysms and hard exudates. No optic nerve abnormalities are seen and visual fields are normal on clinical testing. The examination is otherwise unremarkable, with normal peripheral pulses and no evidence of neuropathy.

**Laboratory Evaluation**

Laboratory test results are as follow:

- Glucose, 182 mg/dL (normal, 70 to 100 mg/dL [fasting])
- HbA1c, 9.8% (normal, 4.0% to 6.3%)
- Thyroid-stimulating hormone (TSH), 1.2 µU/L (normal, 0.3 to 5.0 µU/L)
- Free thyroxine (FT4), 0.8 ng/dL (normal, 0.8 to 1.8 ng/dL)
- Luteinizing hormone (LH), 1.5 U/L (normal, greater than 30 U/L [postmenopausal])
- Estradiol, 22 pg/mL (normal, less than 35 pg/mL [postmenopausal])
- GH, 52 ng/mL (normal, 0 to 10 ng/mL)
- IGF-1, 532 ng/mL (normal, 90 to 360 ng/mL)
- Adrenocorticotropic hormone (ACTH), 12 pg/mL (normal, 10 to 60 pg/mL)
- Cortisol, 12 µg/dL (normal, 7 to 25 µg/dL [morning])
- Prolactin, 41 ng/mL (normal, 4 to 30 ng/mL [postmenopausal])

**Presumptive Diagnosis**

Acromegaly is suspected in this patient, and elevated fasting GH and IGF-1 concentrations support the diagnosis.

- **Does this patient require further evaluation before proceeding to treatment for acromegaly?**

This patient’s clinical features are strongly suggestive of acromegaly with secondary diabetes and hypertension, and results of initial testing are consistent with this diagnosis. GH itself is not reliable as the sole screening test for acromegaly because of the pulsatile release of GH. Even in healthy adults, GH concentrations as high as 50 ng/mL occasionally can be detected. IGF-1 is a more reliable indicator and is regarded as a cost-effective screening test for acromegaly. However, the gold standard for diagnosis is an oral glucose tolerance test, with failure of suppression of GH secretion to less than 2 ng/mL being diagnostic for acromegaly. Magnetic resonance imaging (MRI) will identify the pituitary adenoma in virtually all cases, and the absence of a detectable lesion should raise the suspicion of an ectopic source of GH-RH as a cause of documented acromegaly.

- **Why is this patient’s prolactin concentration elevated?**

Increased prolactin concentration is seen frequently among patients with acromegaly and occurs for one of two reasons. The first possibility is a tumor that cosecretes GH and prolactin. This cosecretion reflects the ontogeny of the anterior lobe of the pituitary gland, with differentiation between the prolactin and GH-secreting cells.
being the final step in development. During dedifferentiation, reversion to this less well-differentiated cell type occurs in a proportion of tumors. The second, more common possibility is that of stalk compression. A large pituitary tumor displaces and compresses the pituitary stalk, impairing the normal inhibitory influence of the hypothalamus on prolactin-secreting cells. In most cases, the rise in prolactin concentration is modest.

**FINAL DIAGNOSIS OF CASE PATIENT**

A glucose tolerance test is performed. Following a 75-g oral glucose load, GH concentration paradoxically rises to 68 ng/mL, confirming the diagnosis of acromegaly. Visual field testing reveals a bitemporal upper quadrantanopia, which was not evident on clinical evaluation. MRI (Figure 2) confirms a large pituitary macroadenoma displacing the optic chiasm superiority.

- How should this patient be treated?

**TREATMENT**

Untreated or incompletely treated acromegaly doubles the age-matched mortality rates for both men and women. Recognized causes of death among these patients include diabetes, vascular disease, hypertension, infection (particularly pneumonia), and colon cancer. Aggressive treatment is indicated in all cases of acromegaly to control the growth of the pituitary mass and to normalize GH secretion and IGF-1 concentrations, if possible. Because of the large size of most causative adenomas, a simple surgical cure is the exception. More commonly, surgical debulking must be followed by adjunctive therapy to achieve and maintain a biochemical cure. Optimally, surgical debulking should leave the residual pituitary intact. Often this is not possible, and panhypopituitarism is a frequent surgical complication affecting up to 20% of patients.

**Surgery**

Of available treatments, transsphenoidal surgery remains the initial treatment of choice, at least for patients with pituitary microadenomas. For larger tumors, which often cause compression of the optic nerves or optic chiasm, surgical debulking is desirable even though cure is unlikely. A transfrontal approach may be necessary.

Transsphenoidal resection usually results in a rapid fall in GH concentrations, with subsequent improvement in the metabolic and growth stimulatory symptoms. In experienced hands, surgery is initially successful in up to 85% of patients with tumors contained within the pituitary fossa. Suprasellar extension dramatically decreases the chance of surgical cure, with fewer than one third of patients with tumors larger than 1 cm achieving surgical cure. Nevertheless, even a debulking procedure may prevent local compression, restore vision in some cases, and dramatically lower (if not normalize) GH hypersecretion.

Pituitary surgery is safe, but possible complications include panhypopituitarism, cerebrospinal fluid leak, injury to the sinuses, meningitis, hemorrhage, and transient or permanent diabetes insipidus. Overall, approximately 15% of patients suffer one or more complications following surgical resection. The risk of these complications increases considerably with large tumors, particularly those that require a transfenral approach.

Even after a surgical cure is achieved, recurrence may occur years after the surgery. Almost certainly, this reflects incomplete tumor resection, with subsequent regrowth of the tumor. The possibility of a second primary tumor arising de novo cannot be fully excluded, however.

**External Beam Radiotherapy**

External beam radiotherapy is no longer regarded as first line therapy for acromegaly because of its slow onset of action. It is more commonly used as a postsurgical adjunctive therapy, particularly when the tumor is large at diagnosis and when resection is incomplete. High energy gamma radiation (the gamma knife) may be useful to treat residual or recurrent tumors within the pituitary fossa. The gamma knife works more quickly than conventional radiotherapy, but the potential for tissue damage limits its use in the proximity of the optic chiasm or cranial nerves.

When external beam radiotherapy is used as primary therapy, it is commonly administered over 4 to 6 weeks at a dose of 50 Gy. Reductions in GH concentrations may be detected within the first year after therapy, but it may take up to a decade to achieve normalization of GH, which occurs in approximately 70% of patients. Shrinkage of the pituitary adenoma is seen over a similar time frame.

The most frequent complication of radiotherapy is the development of panhypopituitarism, which eventually affects half of all patients treated this way. In addition, cranial nerve palsies, hemorrhage, pituitary apoplexy, and impaired short-term memory have all been reported.

**Pharmacotherapy**

Bromocriptine. Bromocriptine is a dopamine agonist that binds to dopamine receptors in the pituitary gland and causes suppression of GH secretion from neoplastic cells. The drug is administered orally in divided doses of 5 to 20 mg daily, although high doses are commonly required to achieve adequate suppression of GH secretion. Bromocriptine often is used following tumor
debunking or pituitary radiotherapy to accelerate resolution of GH excess. Side effects include nausea and vomiting, postural hypotension, headache, vasoconstriction, nightmares, and mood changes. These effects are dose-related and may be minimized by starting at a low dose and increasing gradually. Because of postural hypotension, the first few doses are generally administered in the evening, with the patient already supine. Effective GH suppression and normalization of IGF-1 are achieved in 20% to 50% of patients, but shrinkage of the tumor is substantially less common. Because bromocriptine is poorly tolerated, particularly in the high doses required to treat acromegaly, it is used infrequently.

**Octreotide.** Octreotide is a synthetic somatostatin analog with a longer half-life than somatostatin itself and substantially higher potency in suppressing GH secretion relative to other hormones. More than 90% of GH-secreting pituitary adenomas express somatostatin receptors, and activation of these receptors inhibits GH secretion and may slow tumor growth. For cases in which surgery is not curative, octreotide provides an excellent chance of restoring GH and IGF-1 concentrations to normal. However, this drug is rarely used as first-line therapy for acromegaly, although it may be useful to shrink a large tumor prior to surgical intervention. It also is not curative because the adenoma cells do not appear to undergo apoptosis but merely are reduced in size. Nevertheless, most patients experience resolution of the symptoms of acromegaly within a few weeks of starting treatment. Octreotide is administered by subcutaneous injection and is now available in a long-acting form, which requires administration only once every 2 weeks.

The main side effect of octreotide therapy is the induction of gallstones, the result of gallbladder stasis, which affects 10% to 20% of individuals receiving this treatment. Screening ultrasonography may be justified, but prophylactic cholecystectomy is rarely recommended. The inhibition of other hormones, particularly insulin, is a theoretical rather than a practical concern. Because of the dramatic lowering of GH concentrations achieved in most patients, the benefits on insulin sensitivity far outweigh any impact on insulin secretion, and diabetes or impaired glucose tolerance improves in the vast majority of patients.

Once again, octreotide is rarely used as the only treatment for acromegaly. Much more often, this drug provides an option for adjunctive therapy following incomplete surgical resection of a large adenoma, frequently while awaiting the impact of external beam radiotherapy. Combined octreotide and bromocriptine treatments may be useful in a minority of patients who fail to respond adequately to either drug alone.

**Growth hormone receptor blocking agents.** Pegvisomant is a novel, genetically engineered growth hormone receptor antagonist that blocks the action of GH on the liver, reducing IGF-1 concentrations. Among patients with uncured acromegaly, subcutaneous administration of 15 to 20 mg of pegvisomant daily is sufficient to normalize IGF-1 in up to 90% of patients, with significant improvements in symptoms and signs of acromegaly. The drug has been well tolerated with few significant side effects in early trials. However, there remains some concern about the possibility of accelerated pituitary tumor growth among patients treated with this agent. Although its place in the management of patients with acromegaly remains uncertain, this agent is likely to be useful in treating patients who remain acromegalic despite surgery, pituitary radiotherapy, and octreotide therapy.

**Combined Newer Therapies**

The role of the newer treatment options remains to be elucidated, and the cost currently restricts their use to patients for whom other therapies have proven ineffective. Nevertheless, a combination of octreotide and pegvisomant presents the possibility of normalizing GH and IGF-1 concentrations in a significantly higher proportion of patients than has been possible in the past.

- How should this patient be evaluated following initial therapy?

  Given the adverse consequences of persistent acromegaly and the incomplete efficacy of all therapeutic options, the definition of a cure requires careful attention. Because GH secretion is pulsatile, an isolated normal or low GH concentration is not adequate confirmation of such a cure. Strictly, proving a cure requires the following: 1) normalization of basal GH concentration, 2) suppression of GH in response to a glucose tolerance test, and 3) restoration of the normal circadian rhythm of GH secretion. This third criterion requires blood draws from the patient at intervals over a 24-hour period, usually to generate a 5-point profile. Due to the possibility of late recurrence, reevaluation on an annual basis may be required for a period of several years. In practice, such a detailed assessment is impractical, except in a few academic medical centers. As such, a more practical approach is to measure IGF-1 and GH concentrations and to ensure these stay well within the normal range. In addition, regular pituitary imaging by MRI is essential to detect any tumor recurrence.

- Does this patient require evaluation for complications of acromegaly?
EVALUATION FOR SEQUELAE

As previously noted, patients with acromegaly are at increased risk for vascular disease because of their multiple vascular risk factors, which often include hypertension, diabetes, and hyperlipidemia. Myocardial infarction and stroke are among the leading causes of premature death among patients with acromegaly. Although both diabetes and hypertension can be improved dramatically following treatment of the acromegaly, the increased vascular risk persists. Thus, an appropriate evaluation must include echocardiography and a stress test. Obviously, aggressive management of residual risk factors is warranted.

Patients with acromegaly also are at substantially increased risk for both premalignant and malignant colon polyps and colon cancer. Presumably, this risk reflects a chronic trophic effect of IGF-1 on the colonic mucosa. Almost half of all patients with acromegaly exhibit colon polyps in some studies, with colon cancer rates close to 10%. Both of these figures are dramatically higher than those in an age-matched healthy population, but screening for colon cancer and colon polyps should be performed in all patients with acromegaly. The presence of skin tags appears to correlate with colon polyp formation, and the presence of three or more such skin tags mandates colonoscopy. How frequently colonoscopy should be performed remains in doubt. Among patients with uncured acromegaly, annual evaluation is certainly indicated. Following biochemical cure, the time course of restoration of normal growth patterns of colonic mucosa remains unknown, and these patients should be offered colon screening every 3 to 5 years indefinitely.

CASE RESOLUTION

Under coverage with intravenous hydrocortisone, the patient undergoes surgical resection of the pituitary adenoma via an endoscopic, transnasal, transsphenoidal route. The surgeon reports a “gross total resection” of the pituitary tumor, but the compressed normal pituitary gland was sacrificed. The patient develops polyuria a few hours postoperatively, and urine osmolality is confirmed to be low at 180 mOsm/kg (normal, 200 to 800 mOsm/kg) when serum sodium is 144 mEq/L. The patient is treated with intranasal desmopressin. She is discharged from the hospital 2 days postoperatively on the following medication regimen: hydrocortisone (20 mg every morning and 10 mg every night), levothyroxine (150 µg once daily), and desmopressin nasal spray (twice daily).

Follow-up 12 Weeks Later

Twelve weeks postoperatively, the patient is well with no further headaches and a dramatic improvement in her symptoms of acromegaly. Her blood pressure has decreased to 128/68 mm Hg and her primary physician has been able to reduce her antihypertensive drugs so that she is now taking only a thiazide diuretic. Diabetes control also is improved, and glipizide has been withdrawn because of frequent hypoglycemia. The patient remains on pioglitazone with an HbA1c of 7.2%.

Visual field testing has returned to normal at this time. Repeat MRI shows postoperative changes only, with no visible residual tumor. Because of persistent fatigue and malaise in the late afternoon, the patient’s hydrocortisone regimen is adjusted to 15 mg every morning, 5 mg at lunch time, and 5 mg with her evening meal. Although her TSH level is not recordable, a consequence of her hypopituitarism, FT1 is normal at 1.6 ng/dL and her dose of levothyroxine is left unchanged. At the patient’s own request, and after full discussion of risks and benefits, oral estrogen is prescribed in the form of a continuous combined estrogen and progesterone preparation. She continues to take the desmopressin nasal spray, adjusting the dose according to symptoms; smaller doses result in polyuria.

Morning GH concentration is undetectable and the IGF-1 is now normal at 260 ng/mL. An oral glucose tolerance test shows a flat GH response, which remains undetectable. Because of her young age and the large size of the tumor with likely incomplete resection, and despite the absence of detectable GH secretion, the patient decides to proceed with the recommended external beam radiotherapy of the pituitary fossa. Because she already has irreversible panhypopituitarism, the risks are felt to be small.

Colonoscopy reveals several adenomatous polyps with dysplastic change but no evidence of colon cancer. An echocardiogram confirms cardiomegaly with left ventricular hypertrophy, possibly related to hypertension, but no regional wall motion abnormality is detected following exercise.

Further Follow-up

The patient tolerates a 6-week course of radiotherapy with no side effects. She returns annually for continued monitoring and remains on full pituitary replacement therapy. Gradually, the phenotypic features of acromegaly improve. At 5 years after the surgery she remains obviously acromegalic, but her diabetes is now in remission and she is no longer taking pioglitazone. Her blood pressure also remains well-controlled on a diuretic. Two further colon polyps have been resected at repeat colonoscopy. The patient is asymptomatic and remains well.
HYPERPROLACTINEMIA

OVERVIEW

Hyperprolactinemia, in most cases the result of a prolactin-secreting pituitary adenoma, causes a reduction in the pulsatile release of gonadotropins from the anterior lobe of the pituitary gland. Clinically this results in amenorrhea, infertility, and galactorrhea in women and decreased libido and impotence in men. Other causes of hyperprolactinemia are recognized (Table 3), including pituitary stalk compression, hypothyroidism, and drugs—most notably antipsychotic agents and illegal drugs, including marijuana.29 Idiopathic hyperprolactinemia also occurs frequently and in some cases represents a stress reaction. Even such minor stressors as a venous blood draw may be sufficient to significantly increase prolactin concentrations in some individuals.

Whatever the cause, the impact of hyperprolactinemia is mediated by hypogonadotropic hypogonadism and by the direct effect of prolactin. The recognized actions of prolactin are limited to breast tissue, where it stimulates the production of breast milk. This action depends on prior stimulation with estrogen and is therefore seen only in premenopausal or estrogen-treated women. In contrast to a frequent misconception, hyperprolactinemia does not cause gynecomastia or lactation in men. The actions of prolactin in men are restricted to secondary events related to hypogonadism.30

Because of the impact on the menstrual cycle, hyperprolactinemia tends to be diagnosed earlier in women than in men. Secondary amenorrhea and infertility are common consequences of a microprolactinoma, which is most commonly diagnosed among younger women. In contrast, the effect of prolactin in men depends on suppression of testosterone production, which appears to be a rather more robust system. Higher circulating concentrations of prolactin over longer periods of time are required to suppress testosterone to a clinically significant degree. As a result, prolactin-secreting tumors diagnosed in men tend to be larger, with a greater likelihood of pituitary compression, suprasellar extension, and compression of the optic chiasm.30

CASE PRESENTATION

Initial Presentation

A gynecologist refers a 26-year-old woman to an endocrinologist for further evaluation of secondary amenorrhea.

### Table 3. Recognized Causes of Hyperprolactinemia

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
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<tbody>
<tr>
<td><strong>Pituitary adenoma</strong></td>
<td>Macroprolactinoma (≥ 1 cm)</td>
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<tr>
<td></td>
<td>Microprolactinoma (&lt; 1 cm)</td>
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<td></td>
<td>Mixed functional pituitary adenoma (most often cosecreting growth hormone)</td>
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<td><strong>Hormonal and physiologic causes</strong></td>
<td>Pregnancy</td>
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<td></td>
<td>Lactation</td>
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<td></td>
<td>Nipple stimulation</td>
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<td>Hypothyroidism (especially profound)</td>
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<tr>
<td><strong>Neuropsychological causes</strong></td>
<td>Emotional and psychological stress</td>
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<td></td>
<td>Depression, anxiety</td>
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<td>Venipuncture</td>
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<td><strong>Drugs</strong></td>
<td>Antipsychotic agents</td>
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<td>Antiemetics (centrally acting)</td>
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<td>Dopamine antagonists</td>
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<td>Marijuana</td>
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<td>Opiates</td>
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<tr>
<td><strong>Other</strong></td>
<td>Pituitary stalk compression</td>
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<td></td>
<td>Idiopathic hyperprolactinemia</td>
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</table>

**History**

The patient is previously healthy, takes no medication, and does not use alcohol or tobacco. She entered puberty at approximately age 11, with menarche at age 12. Her periods were initially regular but became scanty and erratic during her first year of college. She was treated with a cyclic oral contraceptive and her periods returned to normal. She married 2 years ago and stopped taking her oral contraceptive with plans for pregnancy. Her menstrual cycle did not return. Despite 18 months of unprotected intercourse, she has failed to become pregnant. The patient saw her gynecologist for further evaluation. Her prolactin concentration was elevated and she was therefore referred for further endocrine assessment.

The patient denies drug use, other than 1 year of occasional recreational marijuana use during college 5 years ago. She has no other symptoms of pituitary disease. She has been aware of scanty breast milk production for 2 to 3 years, which has not been troublesome.
Physical Examination
The patient appears healthy and well. Secondary sexual characteristics are normal. There is scanty, white breast milk expressible with breast compression. The patient is clinically euthyroid with normal visual fields and no features of pituitary disease. Pelvic examination is entirely normal.

Laboratory Evaluation
Laboratory test results are as follow:

- TSH, 2.1 µU/L (normal, 0.3 to 5.0 µU/L)
- FT₄, 1.3 ng/dL (normal, 0.8 to 1.8 ng/dL)
- LH, 0.4 U/L (normal, 1 to 16 U/L [premenopausal])
- Estradiol, 51 pg/mL (normal, 35 to 400 pg/mL [premenopausal])
- GH, 2 ng/mL (normal, 0 to 10 ng/mL)
- IGF-1, 225 ng/mL (normal, 114 to 492 ng/mL)
- ACTH, 45 pg/mL (normal, 10 to 60 pg/mL)
- Cortisol, 14 µg/dL (normal, 7 to 25 µg/dL [morning])
- Prolactin, 163 ng/mL (normal, 4 to 30 ng/mL [premenopausal])
- Pregnancy test, negative

What is the differential diagnosis?

Approach to Diagnosis
The causes of hyperprolactinemia are shown in Table 3. Borderline elevation of prolactin is a common consequence of stress, and sometimes repeat prolactin measurements are necessary to confirm hyperprolactinemia. Exclusion of hypothyroidism as a cause of prolactin excess is essential and is easily accomplished by measurement of TSH level. More difficult is the identification of exogenous triggers, particularly drug effects. Many antidepressants and antipsychotic agents increase prolactin secretion, as do several other legal and illegal drugs in widespread use.29

Once hyperprolactinemia is confirmed, imaging of the pituitary gland, preferably with MRI, is essential to identify any adenoma. Most often in young women, the cause is a microprolactinoma (ie, a tumor less than 1 cm in maximum dimension isolated to the pituitary gland and without significant mass effect). In older patients and particularly in men, a macroprolactinoma may be seen, and the possibility exists of pituitary compression and suprasellar extension.

What are the consequences of untreated hyperprolactinemia?

Clinical Course
Hyperprolactinemia causes no recognized direct effects in men or in postmenopausal women who are not being treated with estrogen. In the female breast primed with estrogen, milk production is caused by high prolactin concentrations, of whatever cause. All of the other systemic consequences of hyperprolactinemia reflect hypogonadotropic hypogonadism. In men, loss of libido and erectile failure are late accompaniments of hyperprolactinemia, often the result of a large macroadenoma. Alterations in body composition including a decrease in muscle mass and an increase in fat mass may ensue, while osteoporosis is common in male hypogonadism.31 Weakness and fatigue are common accompaniments to hypogonadism in men in particular, and both sexes are prone to osteoporosis following sex steroid withdrawal. Among women, osteoporosis arises as part of the normal postmenopausal state in the absence of estrogen replacement therapy. Measurement of bone mineral density may guide the need for specific bone-oriented therapy.

A large macroadenoma may cause direct pituitary compression and rarely causes hypopituitarism. Suprasellar growth distorts and compresses the optic chiasm leading to bitemporal hemianopsia. In contrast, microprolactinomas rarely cause significant consequences beyond the induction of hypogonadism.

How should hyperprolactinemia be treated?

Treatment
The goals of therapy largely depend on the clinical presentation. Because hyperprolactinemia itself carries few consequences other than hypogonadism, and because hypogonadism can be treated with sex steroid replacement, not every patient with hyperprolactinemia requires specific therapy to normalize the prolactin concentration. In particular, elderly patients in whom the diagnosis of a microprolactinoma is made incidentally may warrant observation alone with serial MRIs to ensure that the pituitary tumor does not grow significantly. However, the consequences of hypogonadism should be assessed, particularly the effects on bone and muscle physiology. Testosterone replacement should be considered for men with hypogonadism secondary to hyperprolactinemia, while the decision whether to begin estrogen replacement in postmenopausal women should probably not be significantly influenced by the finding of hyperprolactinemia.

In younger patients, particularly young women with amenorrhea, infertility, and galactorrhea, specific treatment designed to normalize prolactin concentrations is
often required. The goal should be to restore both a normal menstrual cycle and normal fertility, when this is desired. However, women with hyperprolactinemia and normal menses are not at risk for osteoporosis; thus, observation alone with these patients is appropriate. The menstrual cycle can be normalized by the use of a cyclic oral contraceptive. This approach can be safe and effective for some women who do not desire fertility and in whom galactorrhea is not troublesome. For most patients, however, specific treatment to return prolactin concentrations to the normal range is desirable.

Because the natural history of pituitary adenomas is not fully understood, their management is largely empirical. Clearly, patients with large compressive pituitary adenomas require decompression, either surgically or medically, to reduce the mass effect and protect vision and residual pituitary function. However, the rate of progression of microprolactinomas to macroprolactinomas is unknown, and monitoring of tumor growth is an essential component of the management of these patients. Specific treatment of the adenoma may be necessary for enlarging adenomas.

As much as possible, exogenous triggers for hyperprolactinemia should be withdrawn. This is not always possible, however, particularly in the context of antipsychotic drug use; many of these patients must be managed in the same way as patients with idiopathic hyperprolactinemia or a prolactinoma.

Idiopathic hyperprolactinemia can be treated with drugs, whereas prolactinomas can be treated by drug therapy, surgery, or external beam radiotherapy. Transsphenoidal surgery is initially effective in most patients with prolactinomas, although late recurrences are frequent. Nevertheless, surgical resection remains the appropriate management for large tumors that threaten vital structures and for tumors that continue to grow despite medical therapy. Radiotherapy is rarely effective alone in restoring prolactin concentrations to normal, and it is associated with high rates of panhypopituitarism, often years after treatment. The role of radiotherapy is largely relegated to the adjunctive management of tumors exhibiting progressive growth in which complete surgical resection is not possible.

The mainstay of treatment for hyperprolactinemia in the last 20 years has been the use of dopamine agonists. Bromocriptine, introduced in 1971, inhibits the synthesis and secretion of prolactin but also slows or reverses tumor growth. Up to 80% of patients with prolactinomas respond to bromocriptine at doses of 2.5 to 5.0 mg two or three times daily, with shrinkage of the tumor and substantial reductions of serum prolactin concentrations. Side effects can be minimized by gradual dose increases and by initial administration in the supine position. However, side effects of nausea, postural hypotension, and headaches limit the use of bromocriptine in a significant minority of patients. Pergolide and cabergoline, both chemically related to bromocriptine, are useful alternatives and may be better tolerated and more effective.

**CASE RESOLUTION**

Following the confirmation of hyperprolactinemia, the patient undergoes MRI, which demonstrates a pituitary microadenoma without significant pituitary compression or stalk deviation. The remainder of her pituitary function is normal. Following discussion of the therapeutic goals and options for therapy, the patient begins treatment with bromocriptine 2.5 mg every night. Initially she develops some nausea, but after a few days this resolves and she is able to tolerate a gradually increased dose of the drug. After 3 months the patient is taking bromocriptine 5 mg twice daily without side effects. A repeat prolactin concentration is 6 ng/mL (normal, 0 to 20 ng/mL [premenopausal]). Two weeks later she begins a menstrual period. Irregular at first, her menstrual cycle gradually returns to normal. Within 6 months she is asymptomatic with normal menses.

Eight months after starting treatment with bromocriptine her periods stop once more. A pregnancy test is positive. After discussion with the endocrinologist, the patient discontinues the bromocriptine. At 6 months gestation, she and her developing baby are healthy, and she has no clinical evidence of enlargement of her pituitary adenoma and no galactorrhea. The patient intends to breast-feed. The decision whether to reintroduce bromocriptine after the delivery will be made once breast-feeding is completed. The patient is aware that, in some cases, pregnancy may be followed by spontaneous resolution of hyperprolactinemia resulting from a pituitary microadenoma.

**REFERENCES**