Hypopituitarism and Central Diabetes Insipidus

Perioperative Diagnosis and Management

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KEYWORDS

• Pituitary tumor • Adrenal insufficiency • Diabetes insipidus • Hyponatremia • Hypopituitarism

KEY POINTS

- Pituitary tumors have the capacity to result in hormone deficiencies and disorders of water metabolism secondary to their unique location.
- The evaluation of pituitary function before surgery is essential both to identify and treat life-threatening pituitary deficiencies and to rule out the presence of a hormone-secreting tumor.
- Patients who have recently received surgery in the pituitary region must be closely monitored for both diabetes insipidus and hyponatremia, so that these disorders may be promptly addressed.
- All patients who have undergone pituitary surgery require a thorough assessment of pituitary function at least 4 to 6 weeks after surgery to identify new deficits and recognize those that may have resolved.

INTRODUCTION

Pituitary tumors represent a unique class of intracranial neoplasms uniquely located to cause mass effect on vital nearby structures including, but not limited to, the pituitary gland and the hypothalamus, which may result in hormone deficiencies as well as disorders of water metabolism. Patients with pituitary lesions may present with hormone deficiencies before surgery, during surgery, or during the weeks following surgery. Disorders of water metabolism most commonly do not present until the postoperative period and usually are transient. The neurosurgeon's challenge is to safely remove the lesion, decompress nearby vital structures, and preserve or restore pituitary function. Close collaboration between neurosurgical, endocrine, and anesthetic teams is vital during the perioperative time period. This article reviews the perioperative evaluation and management of hormone deficiencies and disorders of water metabolism in patients with lesions of the pituitary region.

PREOPERATIVE ENDOCRINE EVALUATION OF PATIENTS UNDERGOING PITUITARY SURGERY

Pituitary tumors comprise approximately 15% of all intracranial neoplasms, and are clinically apparent in 18 per 100,000 persons.[1] The evaluation of pituitary function before surgery is essential both to identify and treat life-threatening pituitary deficiencies and to rule out the presence of a hormone-secreting tumor. Approximately 70% to 90% of patients with nonfunctioning pituitary macroadenomas have deficiencies in 1 or more pituitary hormones before surgery.[2] The evaluation requires assessment of the following anterior pituitary hormones: luteinizing hormone (LH), follicle-stimulating hormone (FSH), growth hormone (GH), prolactin, adrenocorticotropic hormone (ACTH), and thyroid-stimulating hormone (TSH).

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Each of these hormones and their downstream mediators must be evaluated as discussed later. The most common deficiencies involve GH and the gonadotropins (LH and FSH). ACTH and TSH deficiencies are less common, but must be addressed before surgery when they occur. Central diabetes insipidus (DI) is present in only about 2% of patients on presentation and ideally is recognized before surgery. Although most nonfunctioning tumors of the sellar region represent nonfunctioning pituitary adenomas, the differential diagnosis of nonfunctioning lesions of the sellar region must be considered (**Box 1**).

HYPOPITUITARISM

The signs and symptoms of hormone deficiencies are often nonspecific and vague. In the interest of both time and resources, laboratory tests to screen for hormone deficiencies are used before surgery with dynamic testing reserved for the postoperative period. **Table 1**. addresses the signs and symptoms of hypopituitarism, along with the diagnosis and treatment pertinent to each hormone deficiency. Current recommendations state that all patients with a pituitary lesion, including asymptomatic patients with an incidentaloma, undergo clinical and laboratory evaluation for hypopituitarism.[3] A typical preoperative panel therefore includes TSH, free T4, LH, and testosterone in men versus FSH and estradiol in women, insulin-like growth factor (IGF)-1, prolactin, and an early morning ACTH and cortisol. Chen and colleagues[4] prospectively evaluated 385 patients with nonfunctioning pituitary adenomas undergoing surgery. Hypothyroidism, hypogonadism, and hypoprolactinemia were found in 36%, 41%, and 18% of patients respectively. GH deficiency (GHD) was suspected in 61%. One-third of the patients with hypothyroidism had hypocortisolism.

Box 1
Nonfunctioning lesions of the sellar region

- Gonadotropin-secreting pituitary tumor
- Null-cell adenoma
- Clinically silent hormone-producing adenoma
- Benign neoplasms
  - Craniopharyngioma
  - Meningioma
  - Chordoma
  - Germ cell tumor
  - Rathke cleft cyst
- Malignant neoplasms
  - Lymphoma
  - Metastatic disease (breast and lung)
  - Pituitary carcinoma
- Infiltrative diseases
  - Sarcoidosis
  - Lymphocytic hypophysitis
  - Granulomatous hypophysitis

Central Adrenal Insufficiency

A random serum cortisol should be drawn between 8 and 9 AM to assess for insufficiency because the hypothalamic-pituitary-adrenal (HPA) axis activity is maximal during this time period. A careful history must be taken to rule out recently administered exogeneous glucocorticoids, because this interferes with the assay and renders the results uninterpretable. A serum cortisol level of less than 6 μg/dL in the morning should prompt the initiation before surgery of glucocorticoid replacement to ameliorate patients symptoms. A value greater than 18 μg/dL makes a diagnosis of adrenal insufficiency highly unlikely.[5] Intermediary values must be interpreted in the clinical context, with consideration of patient's symptoms, size and location of the lesion, and the presence of other hormone deficiencies. An intermediary level in the presence of additional hormone deficiencies should prompt initiation of glucocorticoid replacement before surgery with appropriate education regarding steroid adjustment in times of illness or additional dynamic testing. Additional testing must still be performed in the postoperative period in all cases.

Central Hypothyroidism

Central hypothyroidism is suspected by a less than normal or low normal free T4 with a low, normal, or slightly increased TSH. Dynamic testing with thyrotropin-releasing hormone (TRH) does not provide any advantage in the diagnosis of central hypothyroidism and may precipitate pituitary apoplexy in patients with macroadenomas.[6] Treatment of suspected central hypothyroidism should be initiated before surgery to minimize perioperative morbidity. Perioperative problems encountered in untreated hypothyroid patients include delayed clearance of anesthesia, electrolyte abnormalities, ileus, a decreased ability to increase respiratory drive, and neuropsychiatric disturbances. Thyroid hormone replacement can be initiated with once-daily oral L-thyroxine. If indicated, it is important to start glucocorticoid replacement before the start of thyroid hormone

Table 1
Diagnosis and treatment of hypopituitarism

Deficiency	Signs and Symptoms	Diagnosis	Treatment
GH	Fatigue, weight gain, decreased exercise endurance, poor sense of well-being, osteoporosis, hyperlipidemia	Serum IGF-1 less than the normal range Hypoglycemia-induced GH <5.1 ng/mL Arginine-stimulated GH<1.4 ng/mL Glucagon-stimulated GH <3 ng/mL	Daily subcutaneous injections starting at 0.4 mg/d (lower in the elderly) Titrate at intervals of 4–8 wk to IGF-1 within midnormal range Not replaced before surgery and contraindicated in presence of residual or enlarging tumor
ACTH	Nausea, anorexia, weight loss, fatigue and malaise, hyponatremia, and hypoglycemia	Preoperative morning serum cortisol <6 μg/dL ACTH-stimulated cortisol <18 μg/dL Hypoglycemia-induced cortisol <20 μg/dL	Oral hydrocortisone 15–20 mg/d, in divided doses with two-thirds given in the morning Dexamethasone 0.125–0.375 mg qhs Prednisone 3–5 mg/d
TSH	Weight gain, fatigue, constipation, menorrhagia, cold intolerance, dry skin, bradycardia	Serum free T4 in lower quartile of normal range or less than the lower limit of normal	Initiate at 1.6 μg/kg and titrate dose to serum free T4 upper half of the normal range
LH, FSH	Mood swings, impotence, vaginal dryness, hot flashes, decreased libido, osteoporosis	LH, FSH Serum free testosterone in men Serum estradiol in women	Cyclic estrogen and progesterone in premenopausal women Testosterone injections, gel, or patches in men Not replaced before surgery

Abbreviations: IGF, insulin-like growth factor; qhs, at bedtime.

replacement to avoid the risk of precipitating an adrenal crisis caused by the resulting increased metabolism of cortisol.

Central Hypogonadism

Hypogonadism is easily detected in premenopausal women by a history of oligomenorrhea or amenorrhea. An inappropriately normal or less than normal FSH in a postmenopausal woman additionally suggests the diagnosis. Treatment should not be initiated before surgery, and may increase the risk of perioperative venous thrombosis. Men with hypogonadism are usually diagnosed by a combination of less than normal testosterone and inappropriately normal or less than normal LH. If symptomatic, treatment may be initiated before surgery following a discussion of risks and benefits, but is generally held in the perioperative period. Continued need for replacement should then be assessed after surgery.

Growth Hormone Deficiency

GH secretion is pulsatile with a short half-life. Its level is undetectable in adults for nearly two-thirds of the day. A single less than normal GH level in an adult therefore does not suggest GHD. Hepatic IGF-1 is regulated primarily by GH and therefore as a single level may be used as a marker of endogenous GH secretion. A less than normal level suggests the presence of adult GHD, although this level may be influenced by nutritional status and age in normal subjects. Although it is helpful to use IGF-1 as a marker of pituitary function together with other laboratories in the preoperative period, reassessment after surgery, potentially with dynamic testing, is necessary before treatment with GH replacement is considered.[6] We therefore advocate assessment of IGF-1 before surgery, together with a single GH level, only if there is clinical concern for a GH–secreting pituitary adenoma.

Prolactin

Exclusion of pregnancy, prolactin-increasing medications, primary hypothyroidism, and polycystic ovarian syndrome is necessary to accurately interpret a preoperative prolactin level. A preoperative prolactin level greater than 200 μg/L in the setting of a tumor greater than 1 cm is diagnostic of a macroprolactinoma. A prolactin level less than this in the setting of a greater than 1 cm lesion is more likely to indicate stalk compression by a nonfunctioning tumor leading to a decrease in prolactin-inhibiting factors. An intermediary level, or an increase in the setting of a microadenoma (tumor<1 cm) may be worthy of a trial of dopamine agonist therapy, which can be both diagnostic and therapeutic. Prolactin deficiency (prolactin less than the lower limit of the normal range) is associated with severe hypopituitarism.[6]

DIABETES INSIPIDUS

The presence of DI is rare in the preoperative patient and should prompt consideration of a diagnosis of craniopharyngioma, Rathke cleft cyst, or an infiltrative process.[7] The synthesis of arginine vasopressin (AVP) occurs in the supraoptic and paraventricular nuclei of the hypothalamus, not within the posterior pituitary gland. Therefore destruction of the posterior pituitary destroys the nerve terminals of the AVP neurons; as this occurs, the site of AVP release shifts more superiorly on the stalk. Thus, slow-growing noninfiltrative lesions such as adenomas are unlikely to result in this complication.[8] The diagnosis is typically made before surgery by the presence of classic symptoms of polyuria and polydipsia with a high normal serum sodium and urine specific gravity less than 1.005, and a positive response to vasopressin treatment. The symptoms of DI may also be unmasked following initiation of glucocorticoid replacement; glucocorticoids inhibit the synthesis and secretion of AVP, thus adrenal insufficiency can result in increased levels of AVP, which are then lowered following initiation of glucocorticoid replacement.

PERIOPERATIVE MANAGEMENT OF PATIENTS WITH HYPOPITUITARISM

All patients who undergo pituitary surgery, whether or not they have a history of central adrenal insufficiency, should be treated during surgery as if their HPA function has been, or will remain, compromised. This condition may occur secondary to disruption of the anterior pituitary, the pituitary stalk, or the hypothalamus at the time of surgery.[9] Confirmation of residual pituitary tissue left in the sella by the neurosurgeon does not ensure preservation of normal pituitary function, because this tissue itself may be damaged.[2]

Most centers use a standardized protocol for perioperative administration of glucocorticoid as well as an early postoperative assessment of continued need for steroid coverage following discharge.[9] These protocols differ from center to center. A typical approach is to administer intravenous hydrocortisone (Solu-Cortef) 50 to 100 mg on the morning of surgery at the induction of anesthesia. This dose is then repeated at the conclusion of the procedure. Hydrocortisone 50 mg intravenously (IV) every 8 hours is then administered for the first 24 hours following surgery. Provided that the patient is making satisfactory postoperative recovery, the dose can then be decreased to 25 mg IV every 8 hours on the second postoperative day. Once patients are able to take oral medications, they may be transitioned to 20 mg of hydrocortisone by mouth in the morning and 10 mg in the afternoon. This dose, or a comparable replacement, is then taken until patients return for their postoperative visit and definitive assessment of the HPA axis with dynamic testing.

Several centers prefer to assess cortisol levels on the second or third postoperative days at least 24 hours after the last day of IV hydrocortisone to determine the need for continued glucocorticoid use after discharge. Although patients with an early morning cortisol level greater than 18 μg/dL rarely require ongoing steroid replacement, levels between 10 and 17 μg/dL are considered indeterminate and recommendations differ between institutions. One approach is to discharge patients with postoperative cortisol greater than 10 μg/dL on no steroid replacement, but provide them with prescriptions for hydrocortisone and educate them on symptoms of adrenal insufficiency. If these occur, patients are instructed to contact their physicians and obtain both a serum cortisol and serum sodium, because the symptoms of postoperative hyponatremia mimic those of adrenal insufficiency. If serum sodium returns less than normal, patients are appropriately treated with fluid restriction, with hospitalization if appropriate. If serum cortisol is less than 10 μg/dL, then hydrocortisone replacement is initiated.[3]

Khan and colleagues[10] advocate that a postoperative day cortisol value greater than 10 μg/dL accurately predicts integrity of the HPA axis and that these patients, within the appropriate clinical context, may be discharged without any glucocorticoid replacement. Each decision must be personalized and the presence of multiple anterior pituitary hormone deficiencies, including disorders of water metabolism, in the postoperative period should prompt discharge on glucocorticoid

replacement regardless of the postoperative cortisol level. The type of pituitary lesion also predicts the likelihood of pituitary dysfunction; for example, patients with craniopharyngioma are more likely to experience hypopituitarism and DI. A morning cortisol level less than 10 μg/dL necessitates discharge on glucocorticoid replacement with instructions on management of the dose during times of illness.[7,11]

Marko and colleagues[12] uniquely prospectively assessed immediate day-of-surgery cortisol levels to assist in determination of the need for steroid replacement on discharge. Results were correlated with Cortrosyn stimulation testing performed 4 to 6 weeks after surgery. An immediate cortisol level of greater than 15 μg/dL was a predictor of adequate postoperative HPA axis function following transsphenoidal surgery, with a sensitivity of 98%, accuracy of 97%, and positive predictive value of 99%. This information may prove to be increasingly valuable as earlier discharges become more the norm.

A Cortrosyn stimulation test in the early postoperative period is not able to detect recent-onset central adrenal insufficiency because it relies on failure of the adrenal glands to respond appropriately to ACTH, which requires the presence of adrenocortical atrophy to develop secondary to ACTH deficiency and takes time. Klose and colleagues[13] showed that, out of 62 patients with a normal 250 μg Cortrosyn stimulation testing 1 week following surgery, 23 patients developed an abnormal response in the next 1 to 3 months. In the early postoperative period, the 1-μg Cortrosyn stimulation test has the same limitations. Changes in HPA function are therefore dynamic and reassessment of HPA function in the first 3 months after surgery is mandatory regardless of the protocol for glucocorticoid replacement used.[9]

The assessment of other anterior pituitary hormone deficiencies is generally reserved for the first postoperative visit. Those patients taking thyroid hormone replacement for preoperative central hypothyroidism should be continued on their thyroid hormone replacement after surgery. In those patients in whom new-onset hypopituitarism may be suspected (for example, a serum cortisol <10 μg/dL in the postoperative period and/or continued postoperative DI at the time of discharge), an assessment with a serum free T4 may be necessary 1 to 2 weeks following discharge, with replacement indicated following a significant decline in the free T4.

POSTOPERATIVE DIABETES INSIPIDUS

Polyuria is common following pituitary surgery; the primary differential diagnosis consists of central DI, hyperglycemia, diuresis characteristic of patients with acromegaly, and diuresis of intraoperative and postoperative fluids. The last 3 of these can adequately be ruled out by patient history and review of the intraoperative and nursing records. A postoperative hypotonic diuresis occurs in nearly one-third of patients immediately following surgery but is accompanied by neither hypernatremia nor excessive thirst.[9,14]

The cardinal clinical features of DI include polyuria, defined as the passage of more than 30 mL of urine per kilogram of body weight in a 24-hour period; dehydration or plasma hyperosmolarity; and intense thirst with resultant polydipsia. Laboratories reflect an increase in the serum sodium toward 145 mEq/L and always a decline in the urine specific gravity to less than 1.005. An increase in the urine specific gravity in the setting of a normal serum sodium should prompt consideration of hyperglycemia and glucosuria; alternatively, a stable or low normal serum sodium in the setting of a urine specific gravity more than 1.005 without accompanying thirst should prompt consideration of postoperative diuresis.

The incidence of DI following pituitary surgery at our institution is 18.5% and typically presents within 24 hours of surgery; this finding is comparable with that reported by other high-volume pituitary centers.[15] Postoperative DI can exhibit 1 of 3 patterns: transient, permanent, or triphasic. Transient DI accounts for most DI following surgery and is characterized by an abrupt onset of polyuria and polydipsia within the first postoperative day and typically resolves within several days to weeks. Minor injury to the posterior pituitary gland with resultant temporary inhibition of AVP release is thought to be the cause. Permanent DI presents similarly but does not resolve within 6 months of surgery and requires lifelong treatment. This condition occurs in approximately 3% of cases.[7] This form of DI results from extensive damage to the neurohypophyseal stalk and/or the hypothalamus and is most often seen in those patients with infiltrative lesions, suprasellar tumors, or in the setting of extensive resections.[14,15] Other predictors of DI include surgery for microadenomas secondary possibly to increased exploration, intraoperative cerebrospinal fluid leak, younger age, male sex, and intrasellar expansion of the tumor.[9]

The triphasic pattern of DI is characterized by an initial phase consisting of polyuria and polydipsia, followed by an interphase consisting of a period of antidiuresis and often hyponatremia, and a third phase of permanent or prolonged DI. The interphase of antidiuresis is thought to result from leakage of AVP from the injured hypothalamic neurons and occurs approximately 1 week after

surgery, lasting 5 to 7 days. Severe hyponatremia may result during this time period, with symptoms including nausea, headache, and anorexia. Patients may experience transient DI followed by this interphase without the development of permanent DI. A full triphasic response is seen in 1.1% of patients and the biphasic response in 3.4% of patients.[14]

The treatment of postoperative DI most commonly involves the subcutaneous administration of aqueous vasopressin (Pitressin). This treatment is often preferred initially rather than desmopressin (1-desamino-8-D-arginine vasopressin; DDAVP) because of its short-acting nature. Most patients require 5 units of Pitressin every 6 to 8 hours. It is best initially to administer the medication on an as-needed basis because of the often transient nature of the DI. A single dose of vasopressin is often sufficient. If the patient continues to require repeated doses of Pitressin, DDAVP at 1 μg administered subcutaneously can then be used instead. This dose can last as long as 8 to 16 hours and should be provided on an as-needed basis. Lower doses are generally used in the elderly. Patients with DI and an intact thirst mechanism should be allowed free access to water (without administration of IV fluids) to allow their thirst to guide adequate replacement.

If DI persists at the time of discharge, a transition to DDAVP tablets or DDAVP nasal spray (provided that nasal packs have been removed) can be made. The nasal spray delivers a dose of 10 μg per spray; most patients start with 1 spray at bedtime, with a second spray added in the morning if necessary to control symptoms. For both the parenteral and intranasal preparations, increasing the dose increases the duration of effect rather than the magnitude.

DDAVP tablets are most effective in the setting of mild symptoms of polyuria and polydipsia, because they have more erratic bioavailability and patients often need larger doses. A typical dosage regimen starts with 0.1 mg twice daily and may be titrated as high as 0.3 mg twice daily. Potential side effects of DDAVP therapy include nausea, diarrhea, and abdominal cramps.

Patients should be appropriately educated on how to dose DDAVP. The purpose of the medication is mainly to keep patients comfortable and to avoid thirst and frequent urination. They should be told to allow their thirst mechanism to guide their fluid intake and to drink only when thirsty. We generally advise patients that DDAVP is meant to be used on an as-needed basis when the following 3 criteria are satisfied: (1) the patient is using the restroom often (every hour); (2) the patient's urine is clear, resembling water; and (3) the patient is experiencing thirst. The treatment of central DI is summarized in **Table 2**.

POSTOPERATIVE HYPONATREMIA

The differential diagnosis of hyponatremia following pituitary surgery may include the interphase of the previously mentioned triphasic response; syndrome of inappropriate antidiuretic hormone (SIADH) as a result of infection, stress, pain, or trauma to the central nervous system; overzealous

Table 2
Treatment of central DI

Formulation	Dosage	Use	Advantages	Disadvantages
Vasopressin (Pitressin)	5 units subcutaneous q6–8 h prn	Postoperative transient DI	Immediate bioavailability Short duration of action	Reaction at injection site Anti-AVP antibodies reported
DDAVP, SQ	1 μg SQ prn	Postoperative DI	Immediate bioavailability	Reaction at injection site
DDAVP, spray	1 spray qhs to 1 BID (10 μg/spray)	Maintenance medication	Allows for variable dosing	Generic formulation requires refrigeration Delivers fixed dose
DDAVP, oral tablets	0.1–0.3 mg PO BID–TID	Maintenance medication	Ease of Administration Alternative when nasal route not feasible	Erratic bioavailability May require large doses to achieve effect

Abbreviations: BID, twice a day; PO, by mouth; prn, as needed; q, every; SQ, subcutaneous; TID, 3 times a day.

administration of hypotonic fluids and/or DDAVP; and cerebral salt wasting. For reasons that are not understood, patients with Cushing disease have nearly a 3-fold higher risk of postoperative hyponatremia.[14] It is additionally important to rule out pseudohyponatremia secondary to hyperglycemia, hypothyroidism, and untreated central adrenal insufficiency. Cerebral salt wasting is characterized by a natriuresis and hypovolemia and is most commonly associated with subarachnoid disease.[15] Thus, these patients typically have high levels of urinary sodium and clinical signs and symptoms of dehydration.

Postoperative hyponatremia occurs in 9% to 24% of patients following pituitary surgery and peaks on the seventh postoperative day.[9,11,15] Most cases of postoperative hyponatremia secondary to inappropriate AVP release (ie, overadministration of DDAVP, SIADH, or the interphase) respond to fluid restriction. The combined oral and IV intake of fluids is typically restricted to less than 500 mL of the 24-hours urine outpatient. We prefer fluid restriction as the sole approach to the management of hyponatremia when the serum sodium exceeds 125 mEq/L. The fluid restriction is discontinued when the serum sodium exceeds 132 mEq/L or if there is clinical evidence of the development of DI. The sudden occurrence of DI indicates the third phase of the triphasic response and may lead to large increases in serum sodium; therapy is often required to control the rate of increase of the serum sodium even in patients who may still be hyponatremic.

A more severe and symptomatic hyponatremia associated with a rapid decline in serum sodium requires more aggressive treatment. Hypertonic saline may be administered to raise the serum sodium 0.5 mEq/L/h, although it may be reasonable to increase this rate to 1 to 2 mEq/L/h (not exceeding a total of 12 mEq/L in 24 hours) in patients with more acute hyponatremia and significant symptoms including change in level of consciousness or seizures. Once serum sodium exceeds 125 mEq/L, the patient may be treated with fluid restriction.

There is a new class of medications available that specifically targets AVP receptors and may be used in patients with hyponatremia attributable to SIADH. Two of these vaptans, conivaptan and tolvaptan, have been approved by the US Food and Drug Administration for treatment of both euvolemic and hypervolemic hyponatremia. There are currently limited retrospective data in the literature on the use of this class of therapeutics in postsurgical patients with sellar lesions. Potts and colleagues[16] published a series of 13 neurosurgical patients with SIADH who received conivaptan; 6 of these patients underwent endonasal transsphenoidal approach for resection of their lesions. Fluid restriction had previously been attempted in all patients and sodium chloride tablets with or without hypertonic saline in half without success. The mean pretreatment serum sodium in this subset was 124.7 $\pm$ 4.4 mEq/L and the mean time to achieve a 6-mEq/L increase in serum sodium was 10.2 $\pm$ 8.9 hours. Although conivaptan is approved as a 20-mg IV loading dose over 30 minutes followed by a 20-mg IV infusion over the next 24 hours, half of these patients responded sufficiently to the single 20-mg loading dose. Hyponatremia did not recur in any of these patients. Wright and colleagues[17] summarized their experience with treating euvolemic hyponatremia with conivaptan in the neurocritical care unit and found a sodium increase of greater than or equal to 6 mEq/L was reached in most patients within an average time of 13 hours. Vaptans should not be administered if there is any clinical suspicion for the presence of cerebral salt wasting because this represents a hypovolemic state. In addition, because of their mechanism of action, vaptans should not be administered to any patient with a history of DI. Side effects of vaptans include hypotension, infusion-site reaction with or without pyrexia, hyperkalemia, increased creatinine, and increased thirst. In neurosurgical patients, there is the additional risk of possible volume depletion that may compromise cerebral perfusion as well as the concern for rapid overcorrection of sodium leading to central pontine myelinosis. The cautious use of conivaptan in this population thus seems safe and effective but should only be used in the setting of careful monitoring of fluid status, blood pressure, and electrolytes.[16,17]

DISCHARGE INSTRUCTIONS FOR PATIENTS WHO HAVE UNDERGONE PITUITARY SURGERY

Patients who are discharged following pituitary surgery face several unique potential endocrine complications as outpatients. They must be made aware of the potential for these and how to appropriately manage each. These complications primarily involve disorders of water metabolism as well as the management of adrenal insufficiency.

Patients who are discharged on glucocorticoids should be advised of the necessary adjustments in times of illness. In general, patients should be asked to double the dose of glucocorticoid in the event of fever greater than 38.1°C. They should be advised to go to the nearest emergency room to receive stress dose steroids if they cannot

take any medications by mouth because of nausea and vomiting. They should also be reminded, if indicated, to hold their glucocorticoid for 24 hours before their postoperative endocrinology assessment so that definitive testing of the HPA axis may be accurately performed.

All patients, regardless of their postoperative course, should be advised on the signs and symptoms of both hyponatremia and DI. However, the latter is unlikely to be apparent following discharge in the absence of other postoperative complications. Patients are advised that headache, nausea, vomiting, confusion, impaired concentration, and muscle aches may be caused by hyponatremia. Excessive urination and thirst may be related to the onset of DI. In each of these cases, patients are advised to contact their physicians immediately.

POSTOPERATIVE EVALUATION AND MANAGEMENT OF HYPOPITUITARISM AND DIABETES INSIPIDUS

All patients who have undergone pituitary surgery should have a thorough assessment of pituitary function following pituitary surgery both to identify new deficits that may have occurred and to identify those that may have resolved. Nearly one-third to one-half of preoperative pituitary deficits resolve after surgery, thus eliminating the need for lifelong hormone replacement therapy.[18,19] Factors associated with the recovery of pituitary function following surgery include the absence of residual tumor on postoperative imaging and no neurosurgical or pathologic evidence of invasive disorders.[18] Mild or recent onset, or clinically silent hormone deficiencies, as well as a complete resection, additionally predict a greater likelihood of regaining pituitary function.[9] The rate of deterioration of pituitary function following transsphenoidal surgery ranges from 15% to 30%.[18,19] Preoperative prolactin levels have been proposed to be a useful predictor of pituitary function after surgery. Patients with a mild preoperative increase in prolactin presumably secondary to stalk compression tend to be more likely to recover pituitary function. The mechanism underlying this finding is hypothesized to be that hypopituitarism in the setting of large adenomas is secondary to infundibular compression impairing the delivery of hypothalamic-stimulating hormones; this is subsequently relieved following surgery.[19]

Central Adrenal Insufficiency

Regardless of the approach taken with glucocorticoid replacement on discharge, all patients should receive a thorough assessment of the HPA axis with dynamic testing 4 to 6 weeks following surgery. Some patients require further testing 3 to 6 months later.

Several dynamic tests are available to assess the integrity of the HPA axis. The most commonly used tests include the standard and low-dose Cortrosyn stimulation test as well as the insulin-induced hypoglycemia test. Dynamic tests should not be performed until at least 4 weeks after surgery because the presence of pituitary edema in the early postoperative period may interfere with pituitary function. In addition, testing earlier may underdiagnose ACTH deficiency, given that adrenal atrophy may not yet have occurred. Patients should continue on any prescribed glucocorticoid until the time of dynamic testing, and are advised to hold steroid in the 24-hour period before testing.

A Cortrosyn-stimulated cortisol less than 18 μg/dL at 30 minutes (1-μg test) or at either the 30-minute or 60-minute time point (250-μg test) confirms central adrenal insufficiency. Although there has been some concern that the 250-μg Cortrosyn test represents a supraphysiologic stimulus and thus may not detect patients with partial insufficiency, there is equal concern that the 1-μg test has low specificity that may in part be explained by incomplete delivery of the dose of Cortrosyn.[20]

In the insulin-induced hypoglycemia test, regular human insulin is administered IV at 0.1 to 0.15 U/kg body weight; failure of the serum cortisol to increase to greater than 20 μg/dL in the following 90 minutes confirms the diagnosis of central adrenal insufficiency. This test is contraindicated in patients with known low baseline cortisol levels and in those patients with a history of ischemic heart disease or seizures. In addition, a physician must remain in attendance throughout the test. For these reasons, this test is increasingly seldom performed.

In the setting of a borderline test (peak serum cortisol 14–18 μg/dL) with the presence of other pituitary hormone deficiencies, daily treatment is continued for partial adrenal insufficiency. In the setting of no other pituitary hormone deficiencies, the patient may be provided with a prescription for glucocorticoids to take only in times of illness, and may be retested again at a later date.

Lifelong glucocorticoid replacement is recommended in patients with confirmed central adrenal insufficiency. Because the production of adrenal mineralocorticoids is regulated by the renin-angiotensin system, patients with central adrenal insufficiency do not require concomitant treatment with mineralocorticoids. As previously mentioned, lifelong therapy can be commenced with hydrocortisone in divided doses typically of 15 to

20 mg daily with two-thirds administered on rising, dexamethasone 0.125 to 0.375 mg at bedtime, or prednisone in doses of 3 to 5 mg/d. The recommended dose of glucocorticoid has trended downwards over the years. Patients receiving hydrocortisone-equivalent doses of less than 20 mg/d do not differ in metabolic endpoints from patients with intact HPA axes. A higher body mass index (BMI) and more unfavorable lipid profile are seen with increasing doses of hydrocortisone.[21]

Because there is no laboratory test to guide the choice and dose of replacement, the treating physician must rely entirely on these guidelines together with patient symptoms of over-replacement and under-replacement. It has been our experience that patients with persistent symptoms of hypocortisolism, particularly in the morning, on hydrocortisone or prednisone benefit from a change to the longer-acting dexamethasone. Patients with adrenal insufficiency are advised to obtain and wear a MedicAlert bracelet or similar form of jewelry stating that they have adrenal insufficiency and are steroid dependent. Patients are also educated regarding the appropriate adjustment of their steroid dose in the setting of injury, illness, and invasive medical procedures.

Central Hypothyroidism

The assessment of the pituitary-thyroid axis following pituitary surgery is straightforward and relies on the measurement of the serum free T4 at the 6-week postoperative visit. A serum TSH is of little value, because patients with central hypothyroidism have been shown to have biologically ineffective TSH that is either normal or greater than normal, as well as a less than normal TSH. Either a less than normal free T4 or a free T4 that has decreased to the lower quartile of the normal range in patients with clinical symptoms of hypothyroidism should prompt the initiation of replacement therapy. Therapy should be initiated following assessment of the HPA axis and after initiation of glucocorticoid replacement, if indicated, to avoid precipitation of an adrenal crisis. Patients taking oral estrogens may require a higher dose. A recent study recommended initiation of L-thyroxine at 1.6 μg/kg once daily with therapy titrated to a serum free T4 in the upper limit of the normal range because this results in a lower BMI and more favorable cholesterol profile.[22] TSH levels are not reliable indicators of adequate replacement in patients with a history of pituitary disease.[2,7]

In patients with preoperative central hypothyroidism, thyroid hormone replacement can be stopped at the postoperative visit and reassessed in 6 weeks in the presence of other indicators of postoperative pituitary function recovery.

Central Hypogonadism

The resumption of menses in women following pituitary surgery indicates a normal gonadal axis. Serum estradiol and FSH levels should be measured if menses does not resume within 3 months of surgery. Replacement therapy with cyclic estrogen and progesterone is indicated in premenopausal women to preserve bone mineral density, libido, sexual function, and to maintain an overall sense of well-being. A variety of options are available for women and should be guided based on their age, medical history, and patient preference. Although most premenopausal hypogonadal women take oral estrogen replacement therapy, evidence exists that this aggravates the waist/hip ratio and that oral estrogens reduce the action of GH on fat mass. In addition, women using oral contraceptives have lower IGF-1 levels and require twice the dose of GH replacement compared with patients receiving transdermal estradiol. Ethinyl estradiol seems to be a greater GH antagonist than other oral estrogens.[23] Postmenopausal women with laboratory evidence of central hypogonadism are the subject of debate regarding the pros and cons of hormone replacement therapy, similar to women with physiologic menopause.

Measurement of the serum total or free testosterone levels in conjunction with LH is required to confirm central hypogonadism in men. We generally prefer an assessment of at least 2 less than normal early morning testosterone levels, including a free testosterone in elderly or obese patients and patients with hyperinsulinemia. Testosterone replacement can be accomplished with regular intramuscular injections, or the application of transdermal patches and gels. Benefits of therapy include maintenance of muscle and bone mass, improvements in libido and sexual function, and improvements in overall sense of well-being. Therapy is not recommended in those patients with metastatic prostate cancer, breast cancer, an unevaluated prostate nodule, prostate-specific antigen greater than 4ng/mL (or greater than 3 ng/mL in men at high risk for prostate cancer), hematocrit greater than 50%, symptomatic benign prostatic hyperplasia, or poorly controlled heart failure. Therapy is selected based on patient preference, cost, and response to therapy. Therapy is titrated to a testosterone level within the midnormal range.[23]

Growth Hormone Deficiency

GHD can result in several nonspecific complaints in patients with a history of pituitary disease,

including fatigue, weakness, decreased exercise tolerance, and weight gain. GH secretion is less likely to recover than gonadotropin, ACTH, or TSH secretion and may not present clinically until several years following pituitary surgery or radiation therapy.[24]

Serum IGF-1 levels are a useful screening test in the initial evaluation of patients with suspected GHD. IGF-1 results that are either low or in the lower quartile of the normal range in a patient with pituitary disease should prompt the performance of dynamic tests to confirm a suspected diagnosis of GHD. The arginine–GH-releasing hormone (GHRH) stimulation test used to be the most commonly used test to assess GH reserve. This test has since been replaced with other dynamic tests because of the increasing difficulty in obtaining GHRH (see **Table 1**). The likelihood of GHD increases in the setting of multiple pituitary hormone deficiencies; the presence of 3 or more other deficits with a low serum IGF-1 level is as specific for the diagnosis of GHD as dynamic testing. Dynamic testing is therefore not always necessary. In contrast, a normal IGF-1 level in patients with other pituitary hormone deficits does not effectively rule out GHD and these patients should always be further evaluated with dynamic testing.[25]

GH replacement is accomplished by the daily subcutaneous injection of recombinant human GH. In most patients, treatment may be initiated at 0.4 mg/d and titrated upwards every 4 to 8 weeks to achieve a serum IGF-1 level in the middle of the age-specific and gender-specific normal range. Women taking oral estrogens typically require higher doses, as do younger patients. Side effects may include fluid retention, arthralgias, and nerve entrapment syndromes and generally resolve with continued therapy. It is now recognized that important interactions occur between GH and other pituitary hormone replacements. Initiation of GH may unmask adrenal insufficiency or increase glucocorticoid requirements. GH may unmask central hypothyroidism or increase thyroxine requirements. Most premenopausal women with hypopituitarism take oral estrogens, which aggravates the metabolic abnormalities of GHD and induces a relative resistance to GH therapy. Alternatively, testosterone and GH replacement in men act synergistically and the combination of the 2 augments the IGF-1 increase. Other pituitary hormone deficiencies must therefore be monitored as well during the titration of GH replacement.[21]

GH replacement is contraindicated in the presence of an active malignancy and should not commence until therapy for the pituitary tumor is completed. Although it has long been a concern, there is still no compelling evidence that GH replacement therapy increases the risk of recurrent pituitary disease.[25]

Central Diabetes Insipidus

Patients with established DI should be evaluated in the weeks and months after surgery to determine whether their treatment is effective and to ensure that continued treatment is necessary. The previously mentioned recommendation that patients withhold their medication until symptoms recur both avoids the unwanted side effect of hyponatremia and provides continued reassurance that the medication is still necessary. Patients with DI are symptomatic when left untreated and report a resurgence of polyuria and polydipsia if their DDAVP is withheld for more than 12 hours.

The chronic pharmacologic management of the patient with DI is summarized in **Table 2**. Patients may note an increased vasopressin dose requirement in the setting of an upper respiratory infection, during a period of allergic rhinitis, and during pregnancy. Patients should be advised to avoid activities and habits that may lead to the ingestion of large amounts of fluids. Examples may include diet recommendations to ingest numerous glasses of water daily, drinking large amounts of beer at parties, and ingestion of hypotonic fluids during vigorous exercise. These scenarios carry a high risk of hyponatremia in patients treated with DDAVP.

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