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Postoperative endocrine management of pituitary tumors

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Pituitary tumors as well as other lesions in the area of the sella turcica are relatively common. The prevalence of clinically apparent pituitary lesions has been estimated to comprise approximately 10% of all intracranial lesions, whereas incidental pituitary tumors are detected in approximately 11% of individuals at autopsy [1–5]. From 1991 to 2001, we have had the opportunity to share in the postoperative management of more than 750 patients with sellar lesions all operated on by the same neurosurgeon (Table 1). It is the purpose of this article to outline a clinical approach to the postoperative endocrine management of patients undergoing surgery for pituitary tumors and other lesions in the area of the sella turcica.

Acute postoperative endocrine management

Postoperative treatment of patients undergoing pituitary surgery involves both nonendocrine and endocrine management. Fortunately, postoperative nonendocrine complications are relatively uncommon and occur in less than 5% of patients. Complications may include worsening of vision as a result of manipulation or bleeding, central nervous system (CNS) hemorrhage, cerebrospinal fluid (CSF) leakage, or meningitis [6,7]. A detailed discussion of nonendocrine management is found elsewhere in this issue.

The most common early postoperative endocrine complications consist of abnormalities in antidiuretic hormone (ADH) secretion and include diabetes insipidus (DI) and inappropriate secretion of antidiuretic hormone (SIADH). In the aggregate, such complications are common (reportedly up to 25% in the case of DI [8,9] and 12%–20% in the case of SIADH [10]).

Regulation of antidiuretic hormone secretion

ADH is a nonapeptide synthesized in the hypothalamic paraventricular and supraoptic nuclei [11]. It is packaged as a precursor hormone in neurosecretory granules and transported down axons to the median eminence and posterior lobe (neurohypophysis) of the pituitary gland, where it matures to the active hormone.

Once released, ADH binds to specific receptors. Specialized V2 receptors on the renal collecting tubules activate a cyclic adenosine monophosphate (cAMP) kinase cascade, promoting insertion of preformed cytosolic aquaporin (water) channels to the cell surface membrane. These channels permit the passive reabsorption of water down a concentration gradient established earlier in the nephron by a countercurrent exchange mechanism [12,13]. In the absence of ADH, the renal collecting tubules have limited water absorptive capacity, with excretion of large volumes of dilute urine as the end result.

ADH secretion is regulated primarily by plasma osmolality and effective circulating blood volume. Sodium is the predominant extracellular cation contributing to osmolality, and minor changes in serum sodium (hence, osmolality) change ADH secretion [14].

Sensitive hypothalamic osmoreceptors maintain plasma osmolality in a normal range between

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Table 1
University of Southern California–University Hospital Surgical Experience for Sellar Lesions from 1991 to 2002 (n = 833)

Tumor type	Macro-adenoma (>10 mm)	Micro-adenoma (<10 mm)	M:F ratio
Non-Functioning	401	4	1.5:2
Functioning			
ACTH	16	70	1 :5
GH	86	10	1.5:1
TSH	7		1 :1
Prl	74	68	1 :1.3
Other Tumors (Lesions)	91		1 :1

Abbreviations: ACTH, adrenocorticotropin hormone; GH, growth hormone; TSH, thyrotropin hormone; Prl, prolactin; M, male; F, female.

Other tumors include: craniopharyngioma (n = 33); Rathke's cleft cyst (n = 31); clivus chordoma (n = 6); sellar meningioma (n = 18); hyperplasia (n = 3); metastatic (0) (breast, prostate, renal); sarcoid–1; fibrosis–1; hemangioma–1.

280 and 290 mOsm/L by varying ADH secretion. Indeed, variations in serum osmolality of only 1% enhance or inhibit ADH secretion. At levels less than 280 mOsm/L, ADH secretion is maximally suppressed, and increases in osmolality result in increases in ADH secretion in a relatively linear fashion [15–19]. Maximal urine concentration occurs at a plasma osmolality greater than 290 mOsm/L.

In addition to serum osmolality, effective circulating volume (generally a reflection of plasma volume) also influences ADH secretion [16]. Left atrial and carotid sinus baroreceptors monitor effective circulating volume and can produce an exponential rise in ADH secretion via the glossopharyngeal and vagus nerves if volume drops by at least 10% [20].

Under normal circumstances, thirst osmoreceptors are stimulated in response to a rise in plasma osmolality to greater than 290 mOsm/L (Fig. 1). Increases in plasma osmolality to greater than the osmotic threshold for thirst, approximately 10 mOsm/L greater than plasma osmolality, cause intense thirst. Thirst-mediated water intake then prevents the development of plasma hyperosmolality [19,21,22].

Other factors that modulate ADH secretion, albeit in minor ways, include catecholamines, angiotensin II, and atrial natriuretic peptide (ANP). Catecholamines affect renal water excretion through endogenous arginine vasopresseur (AVP) release either by β-agonist stimulation or α-agonist suppression [23,24]. Centrally, norepinephrine fibers cause α-agonist stimulation of ADH release. Angiotensin II directly stimulates ADH, producing neurons, whereas ANP indirectly inhibits ADH secretion [25,26].

Postsurgical diabetes insipidus

DI is a polyuric state characterized by an insufficient or absent secretion of ADH, resulting in

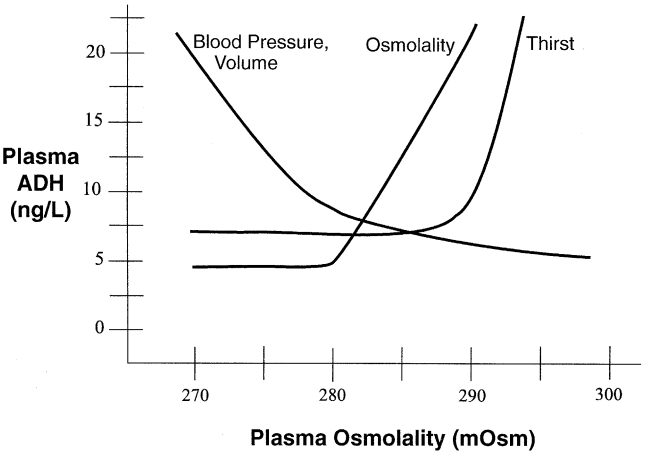

Fig. 1. The influence of plasma osmolality, blood volume and pressure, and thirst on plasma antidiuretic hormone (ADH). Note that the threshold for thirst-mediated ADH secretion is higher than that for serum osmolality and that both low blood pressure and volume cause a significant rise in ADH secretion. (*Adapted from* Robertson GL, Berl T. Water metabolism. In: Brenner BM, Rector Jr FC, editors. The kidney. 3rd edition. Philadelphia: WB Saunders; 1986. p. 385–432; with permission.)

serum hyperosmolality and dilute urine [27–29]. In patients undergoing transsphenoidal surgery, it results from impairment in transport or release of ADH from damage or destruction along the hypothalamus-pituitary axis or to the posterior pituitary gland itself.

DI is the most common endocrine complication after surgery for lesions in the area of the sella turcica, including pituitary tumors, craniopharyngioma, and Rathke's cleft cysts [10,30]. In one large series of 1571 patients with pituitary adenomas who underwent transsphenoidal surgery, 31% of the patients developed DI within the first 24 hours after surgery, 17% continued to have polyuria 3 days after surgery, and persistent polyuria occurred in 6% of the patients 1 week after surgery [31]. Others have reported the postoperative incidence of DI to range between 10% and 20% after transsphenoidal surgery for adenomas limited to the sella turcica and as high as 60% to 80% after removal of large tumors [32]. In our 10 years' experience of more than 750 patients undergoing transsphenoidal surgery, approximately 20% developed DI after surgery.

Clinical presentation

Postsurgical DI is characterized by an abrupt onset of polyuria and thirst, usually within the first 24 to 48 hours after surgery, although, it may occasionally occur later. When untreated, the polyuria may range from a relatively modest 4 to 6 L in 24 hours in the case of mild ADH deficiency to up to 18 L/d if there is complete absence of ADH [33,34]. The severity of DI is dependent on the extent of the damage to the hypothalamic-posterior pituitary unit.

Thirst is a prominent and constant symptom of DI. Indeed, the absence of thirst in the alert patient is evidence against the diagnosis of DI and would favor an alternative cause for the polyuria. Interestingly, patients with DI express a specific preference for ice-cold fluids. This is explained in part by the oropharyngeal reflex produced on fluid ingestion that promptly suppresses ADH release. Drinking cold fluids seems to elicit a stronger reflex response compared with drinking warm fluids [35].

When access to water is limited or interrupted, volume depletion and hyperosmolality can develop and lead to neurologic symptoms, including irritability, lethargy, confusion, and even coma [36]. Because patients are carefully monitored in the early postoperative period, significant volume depletion is unlikely.

Laboratory findings

The biochemical diagnosis of postoperative DI is established by demonstrating serum hyperosmolality in the presence of hypo-osmolar urine. To detect the early onset of DI, we routinely obtain serum electrolyte values within the first few hours after surgery and daily thereafter but more frequently if the clinical situation dictates. In addition, urine specific gravity is checked routinely every 12 hours, and urine output is carefully monitored. Our approach is to obtain serum electrolyte values if the urine output is greater than 300 mL/h for 2 consecutive hours and if the urine specific gravity is 1.005 or less. Under these circumstances, if the serum sodium value is greater than 146 mEq/L, DI is the likely diagnosis. Noteworthy is that the serum sodium in alert postoperative patients usually does not exceed 150 mEq/L, because the normal osmotic stimulus for thirst leads to an increase in fluid intake. This differs in patients who are not alert or who have hypothalamic lesions that would impair normal thirst-stimulated fluid intake [37].

We employ a similar monitoring protocol once the patient has been transferred from the intensive care unit to the ward. Patients are instructed to void in a container, and the nursing staff record the volume of each voiding. In addition, serum electrolytes are assessed every 24 hours until hospital discharge.

It should be noted that patients with poorly controlled diabetes mellitus with glycosuria may have high urine output. The urinary specific gravity (or osmolality) in patients is increased and therefore misleading. Checking for glycosuria in such patients is important so as to ensure that the specific gravity is not falsely increased. Similarly, the serum sodium level may be artifactually decreased in patients with hyperglycemia. Hence, serum glucose should be measured as part of the electrolyte panel in patients who have diabetes mellitus or functioning tumors known to be associated with hyperglycemia, such as those associated with Cushing's disease or acromegaly.

Nearly all patients who develop DI experience a relatively abrupt onset of increasing urine output between 12 and 24 hours after surgery. In most patients, DI resolves spontaneously within 24 hours without specific therapy. On occasion, DI develops later after surgery, and our observation has been that those individuals who develop DI beyond the first 24 to 48 hours are more likely to develop permanent DI.

Postoperative DI often exhibits a triphasic pattern: Initially, it is characterized by polyuria and polydipsia occurring within the first 2 days after transsphenoidal craniotomy and lasting a few days. This first phase is thought to be the result of injury to the neurohypophysis with inhibition of ADH release or release of a biologically inactive ADH-like peptide hormone [29,33,38]. A period of antidiuresis and hyponatremia develops, usually 1 week after surgery. This second phase is also transient, however, and results from ADH leakage from degenerating neurons [29,33,38]. A final polyuric phase then occurs, resulting in permanent DI [29,33,38].

The development, degree, and duration of postoperative DI relate to the site and extent of injury. Lesions high in the pituitary stalk or above the median eminence are more often associated with permanent DI; hence, there is a greater propensity for patients with craniopharyngioma or Rathke's cleft cysts to develop permanent DI [30].

Treatment of diabetes insipidus

Treatment of postoperative DI is aimed at restoring osmotic homeostasis, decreasing urinary output, and repleting intravascular and intracellular volume. Mild DI with urine output no greater than 4 to 6 L every 24 hours and with a serum sodium level less than 150 mEq/L usually requires no specific treatment. With an intact osmotic stimulus for thirst and unlimited access to water, patients drink sufficient amounts of water. Thus, initial therapy may consist of only oral fluid replacement. If the patient is unable to keep up with fluid losses by drinking, intravenous 5% dextrose in water should be administered in quantities sufficient to replenish deficits and keep up with urinary losses. It is important to point out that careful hemodynamic monitoring and assessment of fluid balance and serum electrolytes are essential, especially during the first 24 hours after surgery.

When DI symptoms are unrelenting during the day or persist through the night so that sleep is interrupted, ADH should be administered in one form or another.

Previously, intramuscular administration of ADH (Pitressin) tannate in oil by intramuscular injection was used. Because of the formation of anti-ADH antibodies and occasional abscess formation at the site of injection, its use has been replaced by the synthetic analogue of ADH, desmopressin (DDAVP) [34]. DDAVP exerts an almost immediate effect within minutes of subcutaneous injection and lasts from 8 to 12 hours without any pressor effect [28,34,39]. In the postoperative patient, a 1-μg subcutaneous dose is almost always sufficient to control symptoms, virtually within minutes after administration. Some physicians administer DDAVP intravenously, but this in unnecessary in the hemodynamically stable patient. The need for additional DDAVP is determined by whether or not polyuric symptoms and hypernatremia recur. In our experience, DI resolves completely in most patients after only one dose of DDAVP.

For patients in whom DI persists after the nasal packs are removed, DDAVP may be administered by nasal spray or calibrated rhinal tube applicator. An initial dose of 5 μg at bedtime usually suffices, and if DI becomes permanent, the dose may be titrated in 5-μg increments for a total of 20 μg/d, usually in two divided doses [34]. A preparation of DDAVP is available in tablet form but is seldom used because of erratic bioavailability and increased dose requirements [34,40].

Regardless of the type of DDAVP used in the treatment of postoperative DI, the clinician must be aware of the risk of hyponatremia, and patients warrant careful surveillance with frequent electrolyte monitoring.

Syndrome of inappropriate antidiuretic hormone secretion

SIADH is a disorder of fluid and electrolyte balance characterized by hyponatremia and caused by excessive and sustained secretion of ADH despite serum hypo-osmolality [41]. It has been reported to occur in approximately 12% to 20% of patients after undergoing transsphenoidal craniotomy for pituitary tumors and is the most common cause of hyponatremia after pituitary surgery (see Table 1) [8,42–45].The sustained ADH released from injured posterior pituitary neurons at the time of surgery results in impaired free water excretion and thus water retention [33,38]. Despite impairment in free water excretion, the renal handling of sodium is intact, because there is no alteration of the renin-angiotensin-aldosterone system or in the secretion of ANP [46]. This means that even mild volume expansion activates intact natriuretic mechanisms, with resultant sodium and water loss, thus maintaining a euvolemic state.

Persistent ADH secretion, regardless of the serum osmolality, implies impairment of the normal osmotic stimulus for ADH secretion. With SIADH, water intake exceeds free water excretion,

and the associated antidiuresis results in an increased urinary sodium excretion and thus urine that is disproportionately hyperosmolar [47–49].

Biochemical and clinical features

The biochemical features of postoperative SIADH consist of hypo-osmolar serum and hyperosmolar urine [50]. The serum sodium value is less than 135 mEq/L and often less than 130 mEq/L. Urine sodium excretion is greater than 40 mEq/L, and the serum uric acid is frequently low, reflecting renal loss of uric acid [51,52]. Noteworthy is that renal function is normal, and serum creatinine may be relatively low, reflecting the mild volume expansion characteristic of this supposed euvolemic state [48,49].

Symptoms of SIADH are frequently absent, and the diagnosis is usually first detected on a postoperative serum electrolyte panel after patients have been discharged from the hospital. Symptoms tend to be dependent on the degree of hyponatremia and the rapidity of the decline in serum osmolality [53]. Typical symptoms may include anorexia, nausea, and headache. More pronounced symptoms may include emesis (which can worsen hyponatremia) and lethargy [54,55]. If hyponatremia is severe and the serum sodium level is less than 115 mEq/L, seizures may occur [54,56].

Differential diagnosis of postoperative hyponatremia

It is important that the clinician be aware of other causes of hyponatremia that may be associated with pituitary surgery (Table 2). Perhaps the major clue distinguishing SIADH from other postoperative hyponatremic states is that the onset is generally much later in SIADH than in other hyponatremic states.

Because of the nature of pituitary surgery, impaired corticotropin secretion with resultant hypocortisolism may mimic SIADH biochemically. Cortisol is a physiologic inhibitor of ADH secretion, and the relative or absolute deficiency of cortisol results in an increase in ADH secretion, thus impairing free water excretion and resulting in hyponatremia [57,58].

Because of the importance of maintaining adequate cortisol secretion, hypocortisolism is the most important disorder to consider in the differential diagnosis of posttranssphenoidal hyponatremia. The clinical features differentiating patients with hyponatremia caused by cortisol deficiency from those with SIADH are not clear-cut, because patients with either disorder often

Table 2
Differential diagnosis of hyponatremic states in the postoperative pituitary patients

Disorder	Clinical features	Volume status	Pathophysiology	Diagnosistic features	Treatment
SIADH	Asymptomatic to neurological symptoms	Euvolemia	Increased ADH release	Hyponatremia U_{Na^+} Serum osm Urine osm	Fluid restriction if $Na^+ = 120$mEq/L or consider hypertonic saline and diuretic if $Na^+ < 120$ mEq/L
Hypothyroidism	Bradycardia, slow mentation, coarse voice	Euvolemia	Impaired water excretion	Serum free T_4	Thyroid hormone replacement
Hypocortisolism	Weight loss, malaise, nausea/emesis, hypotension	Hypovolemia	Impaired water excretion	Hyperglyciemia Serum cortisol Blunted cosyntropin test	Glucocorticoid replacement
Diabetes Mellitus	Polyuria, polydypsia	Euvolemia or hypovolemia	Dilutional (pseudohyponatremia)	Hyperglycemia	Correction of serum glucose
Cerebral salt wasting	Weight loss, Tachycardia	Hypovolemia	Renal Na^+ loss	U_{Na^+} CVP	Hypertonic saline, volume replacement

Abbreviations: SIADH, syndrome of inappropriate antidiuretic hormone; U_{Na^+}, urinary sodium; ADH, antidiuretic hormone; Osm, osmolality; T_4, thyroxine; Na^+, sodium; CVP, central venous pressure.

have nausea and anorexia. Cortisol-deficient patients tend to have relative hypotension and postural blood pressure changes, however, and these findings are not present with SIADH. Moreover, the hyponatremia associated with glucocorticoid deficiency usually occurs within 1 or 2 days after surgery in contrast to SIADH, which has its onset later. Also, if patients with known hypopituitarism develop hyponatremia and postoperative doses of glucocorticoid have been adequate, the likelihood of SIADH is low unless there is a supervening illness causing relative cortisol deficiency.

If hyponatremia caused by hypocortisolism is suspected, a random serum cortisol sample should be drawn and an intravenous bolus of 50 to 100 mg of hydrocortisone should be administered. Alternatively, a short cosyntropin (Cortrosyn) stimulation test may be performed before steroid administration. The clinical response in terms of reversal of symptoms and improvement in blood pressure with glucocorticoid therapy in the cortisol-deficient patient is dramatic, often within minutes, whereas no change would be observed in the patient with SIADH. It should be stressed that if cortisol deficiency is suspected to be the cause of hyponatremia, it is safer to treat the patient with steroids pending laboratory confirmation.

Severe hypothyroidism may be associated with hyponatremia. With hypothyroidism, there is decreased cardiac output, causing the carotid sinus baroreceptors to become activated, with increased secretion of ADH [59]. In addition, hypothyroidism is associated with decreased clearance of ADH. The combination of decreased cardiac output and decreased clearance of ADH leads to impairment of free water excretion [60].

The presence of hypothyroidism is generally evident clinically and/or biochemically before surgery, but if untreated or only partially treated, hyponatremia is more likely to occur after surgery. The postoperative administration of free water to patients with hypothyroidism significantly increases the likelihood of hyponatremia [61].

Certain drugs, including serotonin reuptake inhibitors, haloperidol (Haldol), amitriptyline (Elavil), and thioridazine (Mellaril), for example, may be associated with SIADH [62]. Such agents, when administered along with intravenous 5% dextrose in water, may enhance the development of hyponatremia.

The development of postoperative pulmonary complications, such as atelectasis, may be associated with SIADH, although hyponatremia caused by ADH release is more often associated with more significant pulmonary disorders, such as pneumonia or acute respiratory failure [63].

Exuberant intraoperative and postoperative administration of fluids, usually in the form of 5% dextrose, may result in early postoperative hyponatremia, although the diagnosis is easily established by examining fluid intake and output records as well as by observing that the urine specific gravity is dilute.

Uncontrolled diabetes mellitus or hyperglycemia associated with Cushing's disease or acromegaly may also be associated with pseudo hyponatremia. Hyperglycemia causes an osmotic shift of water from the intracellular space to the extracellular space, resulting in a dilutional decrease in serum sodium [64].

Cerebral salt wasting, a rare disorder after pituitary surgery, is reported to be associated with hyponatremia and natriuresis [53,56,65,66]. It is almost always associated with severe cerebrocortical disease, such as subarachnoid hemorrhage [44,56]. Clinically, patients with cerebral salt wasting are volume depleted in contrast to the euvolemia typical of patients with SIADH. Moreover, there is biochemical evidence of dehydration, including an increased hematocrit, serum blood urea nitrogen (BUN), creatinine, and uric acid [56,65]. The diagnosis of the disorder may only be made with certainty by assessing the volume status of the patient with central venous pressure measurements [67].

Treatment of postoperative syndrome of inappropriate antidiuretic secretion

Appropriate treatment of postoperative SIADH takes into consideration several factors, including the degree of hyponatremia, the rate at which it develops, and the presence and severity of symptoms as well as comorbid conditions [54,68]. The goal of therapy is to correct the serum sodium and plasma osmolality and to return the intracellular volume to normal.

The mainstay of therapy of SIADH is fluid restriction and, sometimes, salt administration [46,69]. If SIADH is mild and asymptomatic, fluid restriction is the only treatment necessary. Fluid intake should be limited to approximately 800 to 1000 mL every 24 hours until the serum sodium level normalizes. Serum electrolytes should be monitored daily or every other day. Because patients have typically been home for several days by the time that SIADH develops, our approach is to have serum electrolytes drawn approximately 1 week after surgery at a laboratory convenient to the patient and to have the results telephoned

or telefaxed to our office. Mild asymptomatic SIADH can usually be managed in the outpatient setting as long as patients are able to adhere to a regimen of fluid restriction. To ensure adherence, patients are asked to record intake and output. Daily serum electrolytes are obtained until the serum sodium normalizes or exhibits a consistent upward trend. Correction of the serum sodium generally takes a few days but may take up to 5 days. Some physicians advocate the use of sodium chloride tablets in conjunction with the fluid restriction, although there have been no carefully controlled studies demonstrating the effectiveness of oral sodium administration.

Hospitalization is indicated for patients with symptomatic hyponatremia, and in addition to fluid restriction, intravenous administration of 3% saline may be necessary. A serum sodium value less than 120 mEq/L, especially if associated with nausea, headache, or altered mental status, warrants its use [54,70]. Care must be taken when correcting severe hyponatremia to avoid the development, albeit unlikely, of central pontine myelinolysis [71,72]. Thus, hypertonic saline should be administered no more rapidly than 0.01 mL/kg of body weight per minute [73]. Also, a monitored setting should be employed for patients with underlying comorbid factors associated with fluid retention, such as a history of congestive heart failure or renal failure. Administration of 3% saline is usually not necessary for more than 12 to 24 hours; during this time, serum electrolytes should be monitored carefully, probably every 12 hours [70].

A loop diuretic like furosemide enhances the effects of hypertonic saline by interfering with the countercurrent concentrating mechanism in the loop of Henle; 20 mg of intravenous or oral furosemide administered once or twice a day suffices and is probably advisable, because fluid overload is thus avoided [74,75]. Once SIADH resolves, it rarely recurs.

Acute postoperative management of patients with known or suspected hypopituitarism

Approximately 70% to 90% of patients with nonfunctioning pituitary macroadenomas have deficiencies of one or more pituitary hormones. The most common abnormalities involve either growth hormone or gonadotrophins and usually do not affect surgical morbidity, whereas untreated deficiencies of cortisol or thyroid hormone secretion may.

The primary endocrine issue in the management of patients with known preoperative hypopituitarism is to ensure that an adequate amount of glucocorticoid is administered in addition to appropriate fluid and electrolyte replacement. At our institution, patients receive pharmacologic doses of glucocorticoid before surgery so that there is an ample amount of steroid available during surgery. The day after surgery (indeed, within hours after surgery), patients typically are taking fluids and a diet; steroids may then be administered by mouth. Our approach is to provide between two and three times the preoperative outpatient replacement doses beginning the day after surgery. By the next day, the dose is tapered to the preoperative level unless there is fever or other complications necessitating higher doses. If there is a low-grade fever, twice the replacement dose should be adequate. If there are more serious complications, the dose may be increased up to 10-fold the average replacement dose. Because the normal adrenal glands are able to secrete approximately 200 to 300 mg of hydrocortisone daily during a period of maximum stress [76], the clinician should be able to judge the required amount of steroid according to the stress involved. If the patient must be taken back to surgery to repair a CSF leak, "stress" doses of steroid would be administered, for example, 100 mg of hydrocortisone intravenously every 8 hours for the first day and then tapered quickly to oral maintenance (Table 3).

At some institutions, glucocorticoids are not administered before surgery. In such circumstances, patients with known hypopituitarism should be treated with stress doses (ie, amounts equal to maximal secretion) of steroids. The induction of anesthesia, for example, is a potent stress to corticotropin secretion [77]; therefore, 100 mg of intravenous hydrocortisone should be ordered "on call" to the operating room. After surgery, steroids may be tapered as described previously, with the patient's clinical status being the primary determinant as to how rapidly the glucocorticoid dose can be reduced.

In addition to treating patients with known hypopituitarism with steroids in the perioperative period, glucocorticoid administration should be administered in any patient in whom impairment of the corticotropin-adrenocortical axis is suspected. Hyponatremia occurring within 1 or 2 days of surgery, relative hypotension, unexplained fever, or symptoms of nausea and anorexia may suggest glucocorticoid deficiency, and in such patients, intravenous administration of 50 to

Table 3
Guidelines for hydrocortisone administration in the post surgical patient

Clinical setting	Hydrocortisone dose	Taper schedule
Maintenance	10–20 mg PO qam 5–10 mg PO qpm	N/A
Illness		
Minor[a]	2–3 times the maintenance dose	Duration of illness, then resume maintenance dose
Moderate[b]	50 mg IV/PO bid	50% qd[d]
Severe[c]	100 mg IV q8°	50% qd[d]
Procedure		
Minor[a]	2–3 times the maintenance dose	Duration of illness, then resume maintenance dose
Moderate[b]	100 mg IV	One dose, then resume maintenance dose
Major[c]	100 mg IV q8°[e]	50% qd[d]

Abbreviations: PO, orally; qam, every morning; qpm, nightly; N/A, not applicable; IV, intravenous; bid, twice daily; q8°, every 8 hours; qd, daily.

[a] Illness: atelectasis, diarrhea, emesis; surgery: lumbar puncture with fenestration, ventriculostomy.

[b] Illness: pneumonia; surgery: ventricular-peritoneal shunt, transsphenoidal craniotomy.

[c] Illness: sepsis; surgery: open craniotomy.

[d] Decrease in dose should be based on clinical and hemodynamic stability.

[e] First dose should be administered on induction of anesthesia.

100 mg of hydrocortisone would be indicated immediately after drawing a serum cortisol sample. Patients with cortisol deficiency exhibit improvement within 30 to 60 minutes after steroid administration. It is preferable to err on the side of safety and to treat with a glucocorticoid, pending the results of the serum cortisol measurement.

Appropriate postoperative management dictates that patients with known preoperative hypopituitarism receive adequate hormonal replacement for deficiencies that could have an effect on perioperative morbidity. Most of the patients referred to our neurosurgical service who were known to have either partial or complete hypopituitarism were taking hormonal medication. Occasionally, patients who appeared "eupituitary" before surgery actually had a decreased corticotropin or thyrotropin (TSH) reserve, which becomes manifest when undergoing the stress of surgery; in circumstances where replacement therapy was lacking or inadequate, it was either initiated or modified. It should also be pointed out that despite the fact that neurosurgeons may be able to determine if there seems to be ample remaining pituitary tissue in the sella, its presence does not ensure that endocrine function is preserved, because the surgical procedure itself may result in damage to normal pituitary tissue.

Acute postoperative endocrine management of patients with functioning pituitary tumors

Cushing's disease

Transsphenoidal surgery is the cornerstone in the management of Cushing's disease. With experienced neurosurgeons, transsphenoidal surgery results in initial cure rates of greater than 80% in patients with microadenomas, whereas initial cures are substantially less for patients with macroadenomas [78–83]. Fortunately, because most patients with Cushing's disease have microadenomas (in our series, 83% had microadenomas [see Table 1]), the likelihood of an initial cure is good. In terms of immediate postoperative steroid management, most patients undergoing surgery for Cushing's disease require glucocorticoid therapy, because corticotropin secretion is inhibited by the hypercortisolemia of Cushing's disease, with tumor removal resulting in an immediate decline in circulating cortisol [84].

On our neurosurgical and endocrine services, patients with Cushing's disease are pretreated with steroids in much the same way that patients with nonfunctioning tumors are; this ensures adequate glucocorticoid coverage throughout the surgical procedure and probably for the first 24 hours after surgery. At some institutions, however, preoperative steroids are not administered, and steroids are even withheld the first day after surgery so as

to assess the clinical response of tumor removal. If there is complete tumor removal, an abrupt decline in cortisol levels results in symptoms of relative adrenal insufficiency, including anorexia, weakness, achiness, and nausea by the morning after surgery. Hypertension and hyperglycemia, if present before surgery, should resolve. If steroids are withheld, a serum cortisol result at the lower limit of detectability obtained approximately 24 hours after surgery is an indicator of a surgical cure [85]. Immediately after the serum cortisol sample has been drawn, glucocorticoids should be administered in higher than usual replacement amounts so as to avoid symptoms and signs of steroid deficiency. A reasonable approach would be to give the equivalent of half a stress dose (eg, 100 mg of hydrocortisone or its equivalent) the day after surgery and then to reduce it by approximately 50% each day until physiologic replacement doses of glucocorticoids are reached. If the patient has significant symptoms of steroid deficiency at maintenance levels, the dose may be increased.

Our approach in the immediate postoperative period is to withhold steroids and to obtain a serum cortisol value the morning after surgery; we confirm the result by administering 1 mg of dexamethasone by mouth at bedtime that day and obtain a fasting serum cortisol value the following morning. Dexamethasone provides adequate steroid replacement to the patient so as to avoid cortisol deficiency as well as assay interference that might occur with preoperatively administered hydrocortisone. Once the serum cortisol sample has been drawn, oral glucocorticoid therapy is initiated with hydrocortisone.

The other aspects of immediate postoperative endocrine management of patients with Cushing's disease center around fluid and electrolyte balance as described for patients with nonfunctioning tumors. Patients with Cushing's disease may be more prone to develop delayed onset of hyponatremia because of relative cortisol deficiency and SIADH [86], although that has not been our experience.

Growth hormone-producing tumors

Early postoperative endocrine assessment of surgical cure in acromegaly includes measurement of serum growth hormone the morning after surgery. A value of less than 2 ng/mL by radioimmunoassay or less than 1 ng/mL by immunoradiometric or chemiluminescent assay suggests an early cure [87,88]. Measuring the serum insulin growth factor-1 (IGF-1) immediately after surgery is not recommended, because it takes more than a week, and sometimes even up to several months, to return to normal after successful surgery [89,90].

Excess tissue fluid is a common feature of growth hormone–secreting tumors, because growth hormone increases renal tubular resorption of sodium [91]. Successful tumor removal leads to prompt reduction of growth hormone levels within a few hours after surgery, resulting in mobilization of excess tissue fluid and a marked diuresis, usually beginning approximately 24 hours after tumor removal [92]. Because of the exuberant excretion of free water, urine specific gravity is low, and the clinician might erroneously suspect the presence of DI. The diuresis associated with successful tumor removal is not associated with either hypernatremia or the thirst characteristic of DI. DI may coexist in patients with acromegaly, however, and careful monitoring of serum electrolytes and fluid balance is necessary. Because hyperglycemia is also common in patients with growth hormone–secreting tumors, successful tumor removal usually results in a prompt resolution of hyperglycemia and no further need for hypoglycemic agents that the patient may have been taking before surgery [92].

The cure rate for patients with acromegaly is approximately 80% for those with intrasellar tumors and significantly lower for those with larger or invasive tumors [36,93,94].

Prolactinomas

Prolactinomas are the most common functioning tumors for which patients undergo transsphenoidal surgery, and nearly all patients with prolactinomas in our series underwent surgery because of adverse side effects from dopamine-agonist drugs. The immediate postoperative endocrine management of patients with these lesions is straightforward and is directed at monitoring of fluid balance and serum electrolytes as described for other pituitary lesions. Because the half-life of prolactin in serum is 20 minutes, surgical cure may be assessed by measuring the serum prolactin level the morning after surgery; a level at the lower limit of detectability ensures an approximately 90% likelihood of long-term cure [7,95]. We generally measure prolactin on 2 successive days because we have occasionally observed a further decline in serum prolactin 48 hours after surgery.

Thyrotropin-secreting tumors

This rare cause of thyrotoxicosis comprises approximately 0.5% to 1% of all pituitary tumors. The hallmarks of the preoperative diagnosis include clinical and biochemical evidence of

hyperthyroidism associated with an inappropriately elevated serum TSH level [96,97]. The diagnosis is further suggested by an elevated serum α-subunit level and is confirmed by the MRI demonstration of a pituitary tumor [98,99]. Specific endocrine management of patients with such lesions is directed toward reversing the catabolic effects of hyperthyroidism before surgery with the use of thionamide blocking drugs as well as minimizing cardiac arrhythmic potential and congestive heart failure during surgery and immediately after surgery. If patients are thyrotoxic during surgery, administration of β-blocking agents may be required to control heart rate. Thyroid storm has not been reported in patients undergoing surgery for such lesions.

A suppressed serum TSH level within 24 hours after surgery suggests successful tumor removal, because the thyrotrophs in the normal remaining pituitary tissue have been suppressed by elevated circulating thyroid hormone stimulated by the tumor. Thyroid hormone concentrations do not fall as rapidly, however, because thyroxine has a serum half-life of 1 week [100].

Postoperative fluid and electrolyte management are the same as outlined for other pituitary lesions.

Early follow-up outpatient endocrine management

Chronic management of postoperative diabetes insipidus

Intranasal DDAVP is the drug and route of choice for the management of chronic DI. A single bedtime dose of 5 μg usually is adequate, although as mentioned, up to 20 μg/d may be necessary, especially if DI is complete [101]. Some physicians favor oral DDAVP because of the ease of administration, but titration may be difficult because of the unpredictable intestinal absorption [102].

Pregnant patients may require higher doses of DDAVP because of the increased degradation of ADH by placental vasopressinase [103,104].

The monthly cost of DDAVP may be prohibitive for some patients, and other options for therapy are available, especially if DI is mild.

Chlorpropamide (Diabinese), an oral hypoglycemic agent, was previously commonly used for the treatment of partial DI [105]. It seems to act by enhancing the renal response to ADH, probably by stimulating cAMP [34]. Its use is limited by the risk of hypoglycemia.

Clofibrate, a hypolipidemic agent, and the antiseizure drug carbamazepine (Tegretol) are both thought to decrease polyuria by enhancing ADH release from the neurohypophysis in patients with partial DI and by enhancing the renal response to ADH [28,34,106].

Thiazide diuretics along with a low-sodium diet have long been employed in the treatment of chronic partial DI and lower urine output by as much as 50% by reducing intravascular volume [34].

Nonsteroidal anti-inflammatory drugs (NSAIDS) have been shown to reduce urine output in patients with partial DI by as much as 25% to 50%, probably by inhibiting the prostaglandin-antagonistic effect on ADH [107].

Nonfunctioning tumors

The primary issue regarding outpatient follow-up endocrine management of patients with nonfunctioning pituitary tumors is whether or not long-term hormonal replacement is necessary. This applies both to patients who were taking hormonal replacement for hypopituitarism before surgery as well as to those who were placed on hormone therapy after surgery. Because there may be some return of pituitary function in patients who underwent adenoma removal [108, 109], endocrine evaluation is recommended between 6 and 12 weeks after surgery.

An elevated serum follicle-stimulating hormone (FSH) level in postmenopausal women or the presence of menses in premenopausal women is strong assurance of normal pituitary function, because gonadotrophins and growth hormone become impaired before corticotropin and TSH [110]. For premenopausal women who have not had resumption of menses, a serum estradiol value should be obtained.

A serum testosterone level should be checked in male patients. A serum level in the normal range for the patient's age is a strong indication of normal pituitary function in men.

For patients with low gonadotrophins or target organ sex steroid levels, the following tests are indicated:

1. A serum free T_4 (or estimate of free T_4) in at least the midrange of normal suggests adequate TSH secretion. A value at the lower limit of normal may be abnormal.
2. A normal fasting serum cortisol level 24 hours after the last dose of hydrocortisone suggests adequate corticotropin function. The test result must be interpreted with caution, however, because of the wide range of normal values. A typical laboratory may

report a normal morning cortisol range between 8 and 25 μg/dL, for example. Most endocrinologists believe that the early morning cortisol level should be at least 15 to 18 μg/dL to be certain of adequate corticotropin reserve. A serum cortisol level less than 3 μg/dL on two separate occasions indicates adrenocortical insufficiency, and no further evaluation of corticotropin reserve would be indicated. Values between 3 and 18 μg/dL require a dynamic test of corticotropin reserve. Traditionally, the cosyntropin (Cortrosyn) stimulation test using 250 μg of cosyntropin was employed; a serum cortisol increase of 10 μg/dL above baseline was considered normal. Recently, however, it was noted that using the "standard" dose of 250 μg of cosyntropin resulted in falsely normal results in some patients who actually had some impairment in corticotropin secretion [111]; cosyntropin stimulation is now being performed more frequently with a dose of only 1 μg administered intravenously after a baseline serum cortisol value is drawn, with a repeat cortisol measurement 30 minutes later. The "low-dose" cosyntropin test is believed to represent a more physiologic corticotropin stimulus [112]. Other dynamic tests of corticotropin reserve, such as the insulin tolerance test (the "gold standard") or the metyrapone test, are infrequently used in clinical practice because both require extremely careful patient monitoring and are cumbersome.

3. Adequacy of growth hormone secretion may be tested by several different methods, including stimulating growth hormone with intravenous arginine, growth hormone releasing hormone, or by the administration of an oral dose of levodopa [113,114]. Details of performing the various tests are beyond the scope of this article; however, when they are indicated, they are generally performed by an endocrinologist. As mentioned previously, the insulin tolerance test is infrequently used.

The presence of otherwise normal pituitary function does not ensure adequate growth hormone reserve. Approximately 45% of patients with pituitary disease and apparent normal corticotropin and TSH function are growth hormone deficient, and the presence of corticotropin or TSH deficiency virtually guarantees that patients are growth hormone deficient [115]. Therefore, when there are multiple hormone deficiencies, growth hormone reserve need not be tested.

The choice of whether or not to assess for growth hormone deficiency in patients with no other apparent hormone deficiencies would depend on whether or not the clinician thinks that long-term growth hormone replacement therapy would be indicated if growth hormone deficiency were present. The clinical relevance of testing growth hormone is that growth hormone therapy is available for adults; patients with adult growth hormone deficiency seem to suffer increased morbidity and perhaps increased mortality [116,117].

It should be pointed out that measurement of fasting or random growth hormone levels or serum IGF-1 levels is not an adequate test of growth hormone reserve.

The presence of DI should be considered in the patient who complains of significant nocturia associated with thirst. Patients initially should be asked to measure 24-hour urine output; if output is greater than 3 L, a water deprivation test may be carried out [118]. A practical approach is to have the patient refrain from drinking fluids during the night and obtain an early morning serum electrolyte panel and urine specific gravity. Patients with DI nearly always have serum sodium levels greater than 143 mEq/L along with urine specific gravity less than 1.005, whereas patients with primary polydipsia virtually never have serum sodium levels greater than 140 mEq/L.

Functioning tumors

Cushing's disease

Follow-up management of patients with Cushing's disease is directed toward tapering and discontinuing glucocorticoid replacement. Patients who do not have evidence of early cure are obviously not treated with steroids. Tapering protocols vary greatly and depend largely on individual patient symptoms. For patients taking hydrocortisone, a reasonable approach would be to decrease the dose by 5 mg/d every week and to obtain a fasting serum cortisol level 24 hours after the last dose. A serum cortisol value less than 3 μg/dL would indicate a persistent defect in corticotropin secretion, and resumption of glucocorticoid therapy would be indicated, followed by repeating the tapering and testing process again. Most patients no longer require postoperative steroid replacement after approximately 3 or 4 months, and, indeed, the longer the requirement for glucocorticoid therapy, the greater is the likelihood of cure

[84]. A fasting serum cortisol level of greater than 20 μg after cessation of steroid therapy would raise the concern of early recurrence; in such circumstances, obtaining a 24-hour urine collection for free cortisol would be indicated [119,120]. Longer term assessment of patients with a history of Cushing's disease is discussed elsewhere in this issue.

Acromegaly

Follow-up endocrine evaluation of patients with growth hormone–secreting tumors consists of assessing the adequacy of surgery by measuring serum IGF-1 levels as well as by evaluating growth hormone dynamics. A serum IGF-1 level should be obtained during the first postoperative visit. A normal result suggests a surgical cure, but long-term follow-up of patients is imperative. Whether or not to follow patients with serum IGF-1 levels alone or in combination with assessments of growth hormone dynamics is unclear and beyond the scope of this article. Because patients with acromegaly usually have macroadenomas, more detailed endocrine assessment may be warranted as described previously in the section on nonfunctioning tumors.

Prolactinomas

Because prolactin decreases almost immediately after surgery, a prolactin determination at the first outpatient follow-up visit provides an excellent assessment as to the likelihood of cure. Because most prolactinomas (in women) are microadenomas, other pituitary hormones are unlikely to be affected and usually do not require investigation unless the clinical situation dictates otherwise.

Thyrotropin-secreting tumors

Resumption of normal thyroid function, including normal TSH and free T4 levels, suggests surgical cure. Because most TSH-secreting tumors are macroadenomas, the possibility of impairment of other trophic hormone secretion may need to be considered as outlined previously.

Summary

Pituitary tumors are common and are often associated with endocrine abnormalities. Furthermore, pituitary surgery itself may result in additional hormonal changes, including impairment of anterior pituitary hormone secretion and, more commonly, abnormalities of ADH regulation. Endocrine management of patients with pituitary or other sellar lesions involves acute hospital-based and longer term office-based evaluation and treatment. In the immediate postoperative period, careful attention must be directed toward sodium and water balance as well as toward recognition of changes in endocrine function. Postoperative measurement of serum hormone levels also helps to determine if resection of a hypersecreting tumor has been successful. To minimize postoperative morbidity, perioperative endocrine assessment and management of patients undergoing pituitary surgery should consist of a team approach, involving both the neurosurgeon and the endocrinologist.

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