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Current best practice in the management of patients after pituitary surgery

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Abstract: Sellar and parasellar masses are a common finding, and most of them are treated surgically *via* transsphenoidal approach. This type of surgery has revolutionized the approach to several hypothalamic-pituitary diseases and is usually effective, and well-tolerated by the patient. However, given the complex anatomy and high density of glandular, neurological and vascular structures in a confined space, transsphenoidal surgery harbors a substantial risk of complications. Hypopituitarism is one of the most frequent sequelae, with central adrenal insufficiency being the deficit that requires a timely diagnosis and treatment. The perioperative management of AI is influenced by the preoperative status of the hypothalamic–pituitary–adrenal axis. Disorders of water metabolism are another common complication, and they can span from diabetes insipidus, to the syndrome of inappropriate antidiuretic hormone secretion, up to the rare cerebral salt-wasting syndrome. These abnormalities are often transient, but require careful monitoring and management in order to avoid abrupt variations of blood sodium levels. Cerebrospinal fluid leaks, damage to neurological structures such as the optic chiasm, and vascular complications can worsen the postoperative course after transsphenoidal surgery as well.

Finally, long-term follow up after surgery varies depending on the underlying pathology, and is most challenging in patients with acromegaly and Cushing disease, in whom failure of primary pituitary surgery is a major concern. When these pituitary functioning adenomas persist or relapse after neurosurgery other treatment options are considered, including repeated surgery, radiotherapy, and medical therapy.

Keywords: Cushing disease, diabetes insipidus, hypopituitarism, hypothalamic hormones, hypothalamic neoplasms, hypothalamo-hypophyseal system, pituitary hormones, pituitary neoplasms

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Introduction

Several masses can involve the hypothalamic–pituitary region, including pituitary adenomas (accounting for the majority of cases), craniopharyngiomas, Rathke's cleft cysts, meningiomas, other rare brain tumors, or infiltrative, infectious, or vascular disease. Pituitary and craniopharyngeal duct tumors are the second most common group of brain neoplasms in the USA (pituitary adenomas most common in adults, and craniopharyngiomas in children and adolescents), accounting for approximately 16% of all primary brain tumors, and being the most common affected sites in adolescents and young adults (about 32%).[1]

While the majority of pituitary adenomas are nonsecreting, the most frequent hormone-secreting tumors are prolactinomas. While prolactinomas are usually treated medically, other secretory pituitary adenomas and nonfunctioning sellar and parasellar masses that cause mass effect symptoms are treated surgically, with a majority of cases performed *via* the transsphenoidal approach. Postoperative care by a multidisciplinary team including neurosurgeons, endocrinologists, and

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intensive care teams is a crucial component of the management.[2] In this review we will analyze the possible complications of pituitary surgery and their management, focusing on the most frequent: hypopituitarism and disorders of water metabolism. Other aspects of long-term surveillance have to be tailored according to the cause that led to pituitary surgery, and this goes beyond the aim of this review. We will focus only on the postsurgical management of acromegaly and Cushing disease (CD), as failure of primary surgery is a major clinical problem and the decision on the best approach for persistent and recurrent disease requires careful evaluation.

Hypopituitarism

One of the most common complications after pituitary surgery is hypopituitarism.[3] This can be partial or total (panhypopituitarism, where all hormonal axes are involved), affecting the anterior pituitary, the posterior pituitary, or both. Moreover, hypopituitarism can be transient or permanent. In this section anterior pituitary hormone deficiency is analyzed, whereas disorders of posterior pituitary are reported later in the manuscript (Table 1).

The risk of postoperative hypopituitarism varies according to case series and the etiology, ranging from 5–25% for pituitary adenomas, and its occurrence varies depending on the operating neurosurgeon's experience.[4,5] It peaks to approximately 75% for craniopharyngiomas.[6] For pituitary adenomas, in addition to experience, the size and consistency of the tumor, the extension of surgical manipulation, and surgery for recurrent disease play a role in the occurrence of hypopituitarism.[4] The rate of pituitary insufficiency is higher for patients operated for CD, and several factors can account for this observation: the long-term need for glucocorticoids (GCs) postoperatively for the onset of adrenal insufficiency (AI), a larger pituitary manipulation during surgery, and the frequent median localization of adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas. Finally, endogenous hypercortisolism can cause growth hormone (GH) deficiency and central hypogonadism *per se*, and these deficits can last for months/years after successful treatment of CD (Table1).

Provided that the postoperative period has been uneventful and no acute complications have occurred (e.g. central AI; see below), the first evaluation for the anterior pituitary function should be performed approximately 4–6 weeks after pituitary surgery (Table 1). Thyroid axis evaluation requires measurement of free thyroxine (T4). Morning serum testosterone is measured in males, while menstrual history (and possibly estradiol measurement) is used in premenopausal women. A low or normal follicle-stimulating hormone (FSH) in a postmenopausal woman is a strong indicator of gonadotrophic dysfunction suggesting hypopituitarism. GH axis can be initially assessed by serum insulin-like growth factor (IGF)-1 level. However, unless IGF-1 is low in the setting of panhypopituitarism, the diagnosis of GH deficiency usually requires failure of at least one GH stimulation test.[3] Patients with a preoperative diagnosis of pituitary insufficiency should be reassessed to confirm the need of hormonal replacement therapy, as this may improve after adenomectomy in a significant percent of patients. Jahangiri and colleagues reported normalization of thyroid, male gonadal, female gonadal, cortisol and GH axis in 36%, 18%, 41%, 29%, and 22% of cases respectively.[7] Such recovery may take time, and it has been demonstrated to be higher at 1 year compared with 3 months after surgery. Interestingly, recovery of adrenal function seems more likely in acromegaly patients compared with nonfunctioning pituitary adenomas.[8,9] The timing for further evaluations should be carried out upon clinical judgment.

Management of AI

Central AI is the most important anterior pituitary deficit that can follow pituitary surgery. It should be promptly recognized, as untreated AI can be a life-threatening condition. The status of the hypothalamic–pituitary–adrenal axis (HPAA) before pituitary surgery accounts for differences in the management of central AI perioperatively and in the long term (Table 2).[10–17]

One of the gray areas in the management of non-CD patients with normal preoperative HPAA is whether to give empiric GC coverage after surgery or to apply a steroid-sparing method, giving GC only if AI develops. To date, existing evidence has not demonstrated the superiority of one of the two strategies, and they are both used successfully in clinical practice.[2] Whatever approach is chosen, we recommend to take several factors into account: the percentage of postoperative AI at each center or each surgeon, the

Table 1. Management of anterior hypopituitarism after pituitary surgery.

	How to make the diagnosis?	How to treat and monitor	Comments
Central AI	**Screening:** Morning serum cortisol and plasma ACTH. 'Normal' laboratory results do not exclude a diagnosis of AI **Confirmation:** Use one (or more) among: • ACTH stimulation test for cortisol: may not be reliable in the immediate months following surgery, as it can provide false-negative results (see Table 2) • Insulin-induced hypoglycemia test Metyrapone test	**Hydrocortisone:** 10–12 mg/m^2/day (usually 15–20 mg) in 2 or 3 divided oral doses OR **Cortisone acetate:** Usually 25–37.5 mg in two divided oral doses OR **Modified-release hydrocortisone (unavailable in USA):** 20–30 mg orally once a day Patients with pre-operative AI or operated for CD require stress doses of hydrocortisone in the perioperative period (see Table 2). Monitoring of steroid replacement therapy is mainly based on checking body weight, blood pressure and quality of life. Plasma ACTH is not useful during follow up of central AI	• Exclude AI before starting LT4: LT4 can cause an adrenal crisis, as it enhances the clearance of cortisol • Exclude AI before starting rhGH: GH can cause an adrenal crisis, as it blocks the conversion of cortisone to cortisol. Patients on cortisone acetate may require higher doses of GC • Treating AI can unmask central DI • Instruct the patients and their caregivers to recognize an adrenal crisis: Medical treatment requires immediate administration of parenteral fluids and hydrocortisone • Instruct the patients and their caregivers to increase the dose of GC in case of stressful events: The actual increase of the dose and the way of administration (oral *versus* parenteral) should be adapted to the severity of the stressful event
Central hypothyroidism	**Screening:** Serum TSH and free T4 **Confirmation (optional):** TRH stimulation test for TSH (TRH not available in USA)	**LT4:** Titrate up to a maintenance dose (usually around 1.6 µg/kg). Monitoring of LT4 treatment is done *via* serum free T4. This should be kept in the middle/upper half of the reference range. Serum TSH is not useful during follow up of central hypothyroidism	• Exclude AI before starting LT4 • rhGH can unmask central hypothyroidism or lead to higher LT4 requirements in hypothyroid patients: rhGH can reduce free T4
Central hypogonadism	Exclude hyperprolactinemia. Normal menses in a premenopausal woman rule out hypogonadism **Screening:** Serum LH, FSH, total AM testosterone (in men), and estradiol (in premenopausal women) **Confirmation:** • For men: Second testosterone level may be needed, and free testosterone and SHBG may be used in selected cases • For premenopausal women: medroxyprogesterone test can be used to confirm estradiol deficiency	• **Testosterone (males):** To be used when the patient is not interested in fertility. Serum total testosterone, PSA and hematocrit are used to monitor testosterone replacement therapy • **Estrogens (females):** To be used when the patient is not interested in fertility. Add progestins if the patient has an intact uterus. The presence of normal menses indicates an adequate estrogenic replacement therapy. The monitoring of late-follicular serum estradiol is optional • **Gonadotropins:** To be used when the patient wants to become fertile	• If possible, in women privilege transdermal estrogen formulations, as they interact less in the case of concurrent GH replacement therapy. In fact, the oral route reduces peripheral sensitivity to GH. • CD can cause hypogonadism *per se*. In such setting, biochemical assessment for central hypogonadism should not be performed before several months since successful pituitary surgery, as the effects of previous hypercortisolism can be long-term.

(Continued)

Table 1. (Continued)

	How to make the diagnosis?	How to treat and monitor	Comments
GH deficiency	**Screening:** Serum IGF-1 (sensitivity decreases with age) **Confirmation:** Use one (or more) among: • GHRH + arginine stimulation test (GHRH unavailable in USA) • Insulin-induced hypoglycemia test • Glucagon stimulation test • Other tests that are used in pediatric patients: Arginine alone; L-DOPA; GHRH alone; clonidine Exclude hypothyroidism, as it leads to blunted responses to dynamic testing Patients with multiple pituitary hormone deficiencies after surgery (>3 axes affected) are very likely to have GH deficiency as well (>95%)	**rhGH:** Start with low doses and titrate up to a maintenance dose, which is usually around: • 0.25–0.55 mg GH/kg/day in children • 0.1–1 mg GH/day in adults • Intermediate maintenance values for transitioning patients Women usually require higher doses than men to achieve similar IGF1 responses to men. Women on oral estrogens have higher rhGH requirements. Consider tapering the dose or switching to transdermal estrogen formulations. Monitoring of GH replacement is based on serum IGF-1 aiming between half and the upper half of the age-adjusted reference ranges. In children growth velocity has to be checked. Quality of life, body weight, waist circumference, and blood pressure are important parameters as well (mostly in adults).	• Exclude AI before starting rhGH. In patients taking cortisone acetate, consider tapering the dose upwards • rhGH can unmask central hypothyroidism or lead to higher LT4 requirements • CD can cause GH deficiency *per se*. In such setting, biochemical assessment for GH deficiency should not be performed before 1–2 years since successful pituitary surgery, as the effects of previous hypercortisolism can be long term.

ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency; AM, ante meridiem; CD, Cushing disease; DI, diabetes insipidus; FSH, follicle-stimulating hormone; GC, glucocorticoids; GH, growth hormone; GHRH, growth-hormone-releasing hormone; IGF-1, insulin-like growth factor type 1; L-DOPA, levodopa; LH, luteinizing hormone; LT4, levothyroxine; rhGH, recombinant human growth hormone; T4, thyroxine; SHBG, sex hormone-binding globulin; TRH, thyrotropin releasing hormone; TSH, thyroid stimulating hormone (thyrotropin).

Table 2. Management of central AI perioperatively and after pituitary surgery.

Clinical scenarios	Management during the perioperative period	Long-term management
Preoperative normality of HPAA	Some centers use empiric preoperative GC coverage until a normal adrenal function is found postoperatively (e.g. by measuring morning serum cortisol approximately 1 week after surgery). Other authors start the treatment only if postoperative AI develops (e.g. by measuring morning serum cortisol either immediately after surgery or on postoperative days 1, 2, or 3). Several cortisol cut-offs have been proposed as to be suggestive of AI, and no clear indication exists.	If the patient has been put on GC in the postoperative period: Retest HPAA 4–6 weeks after surgery. Assessment is usually performed by: 1. SCREENING: Measure morning serum cortisol before the first AM dose of the GC: • <138 nmol/l (5.0 μg/dl): HPAA recovery is unlikely. The patient is kept on replacement therapy and retested after several weeks/months • 138–414 nmol/l (5.0–15 μg/dl): HPAA recovery is usually assessed *via* provocative testing (see below) • >414 nmol/l (15 μg/dl): HPAA is very likely and GC therapy can be stopped without further testing 2. CONFIRMATION (PROVOCATIVE TESTS): - Insulin-induced hypoglycemia test: It is the 'gold standard' to assess HPAA recovery, especially in those with partial ACTH deficiency or recent pituitary damage (<1 month). However, this test is cumbersome, time-consuming and stressful for the patient. It is contraindicated in the elderly and those with cardiovascular, cerebrovascular, or seizure disorders - ACTH stimulation test for cortisol: It is the most widely used test. Two different doses of synthetic ACTH can be used: A standard dose (250 μg) or a low dose (1 μg) - Metyrapone test: It is a reliable test, but its use is not widespread worldwide N.B. ACTH stimulation test can be unreliable in patients with partial AI or recent pituitary damage (< 1 month). Therefore, is should not be used in the immediate postoperative period. If a provocative test is needed and insulin-induced hypoglycemia and metyrapone testing are contraindicated or not available, the patient should be kept on replacement therapy. An ACTH stimulation test can therefore be planned later on during follow up. If the patient has not been placed on GC in the postoperative period: Instruct him or her and their caregivers to monitor any signs and symptoms of AI in the immediate days following discharge. Give instructions to take parenteral hydrocortisone, if necessary. Retest HPAA 4–6 weeks after surgery (see above).
Diagnosis of central AI before pituitary surgery	Give replacement doses of GC (see Table 1) until the day of surgery. Give stress doses of GC (e.g. 50–100 mg of parenteral hydrocortisone or 2–4 mg of parenteral dexamethasone) at the time and immediately after surgery. Gradually reduce the dose of parenteral GC, returning to the preoperative replacement oral therapy in 48–72 h, provided that the postoperative period is uneventful.	The chances of HPAA recovery after pituitary surgery are very low. The patient is extremely likely to need lifelong GC replacement therapy. A single postoperative morning serum cortisol (before taking the first dose of GC) can be sufficient to confirm persistent AI.

(Continued)

Table 2. (Continued)

Clinical scenarios	Management during the perioperative period	Long-term management
Preoperative diagnosis of CD	Give stress doses of GC (parenteral hydrocortisone or, as an alternative, dexamethasone) at the time and immediately after surgery. Gradually reduce the dose of parenteral GC, until switching to replacement oral therapy (see Table 1) in 48–72 h, provided that the postoperative period is uneventful.	Transient AI is expected after curative surgery for CD. The development and degree of hypocortisolism are the most useful tools for predicting remission and recurrence. The median duration of AI of patients in persistent disease remission is approximately 1.5 years, but it can vary widely. Factors potentially affecting the duration of AI after successful treatment for CD are: • Duration of signs and symptoms before surgery: The longer it is, the longer the duration of AI • Age at diagnosis of CD: Contrasting results have reported, with studies reporting either a direct or an inverse correlation between age at diagnosis and the duration of AI. Pediatric patients seem to be recover HPAA rather quickly • A large amount of Crooke's cells in the para-adenomatous tissue, an extensive pituitary surgical manipulation, and the medial localization of the adenoma usually predict a longer need for GC replacement therapy Long-term treatment of AI with physiological replacement doses of GC: Please note that: • The patient may have persistent CD after surgery (see Figure 3): if that is the case, GCs have to be stopped and further treatment options considered • The patient may develop a 'GC withdrawal syndrome' immediately after surgery: it can last up to 6–12 months and is characterized by self-limiting symptoms resembling AI despite an adequate GC replacement therapy. Common complaints include fatigue, nausea, dizziness, lethargy, arthralgia, myalgia, and flu-like symptoms. Psychiatric symptoms can rarely occur. The actual causes of this syndrome are currently unknown. Patients might benefit from the temporary use of higher doses of GCs, or from slower tapers down to oral replacement doses in the postoperative period Periodically test HPAA recovery (see above): • Morning serum cortisol • Provocative testing Stop GC when (and if) biochemical tests show either HPAA recovery or CD recurrence

ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency; CD, Cushing disease; GC, glucocorticoids; HPAA, hypothalamic-pituitary-adrenal axis.

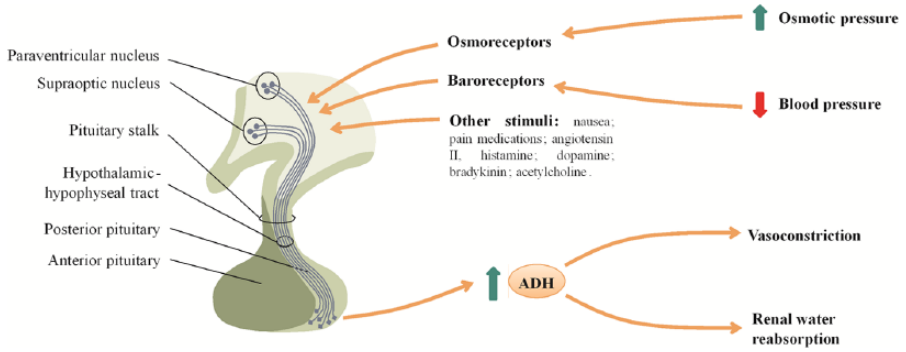

Figure 1. Physiology of ADH release and action. ADH is synthetized in the magnocellular neurons of the paraventricular and supraoptic nuclei, transported along the axons of hypothalamic neurons, and stored in the posterior pituitary. Its release has two major stimuli, a raise in plasma osmolality and a decrease in blood pressure and circulating blood volume. After ADH is secreted in the circulation, it acts both on kidneys (by promoting water reabsorption at the renal collecting duct) and on blood vessels (by stimulating vasoconstriction).
ADH, antidiuretic hormone.

expertise of the team taking care of the patient after surgery, the extent of surgery, the postoperative course, and the turnaround time of serum cortisol measurements at the institution. Because postoperative AI, although relatively rare in those with an intact HPAA before surgery who are referred to experienced neurosurgeons, remains a life-threatening condition if not promptly recognized and treated, we give parenteral hydrocortisone to all patients in the first 24 h after pituitary surgery (e.g. 50 mg every 6 h), rapidly tapering to the standard oral replacement dose (15–20 mg/daily) during the following 48 h if surgery is uncomplicated. This dose is similar to what was recommended in a study looking at urinary free cortisol secretion in patients with intact HPAA (150 mg/day).[18] We then check an AM prehydrocortisone dose serum morning cortisol in an outpatient setting about 1 week after surgery. A level <138 nmol/l (5.0 µg/dl) highly likely predicts AI, whereas values >414 nmol/l (15.0 µg/dl) virtually rule out this diagnosis in all patients.[2,14] However, different diagnostic cut-off points for morning serum cortisol have been proposed by various investigators, with the optimal diagnostic cortisol cut-off point remaining an issue of debate.

For low (<138 nmol/l, 5.0 µg/dl) or intermediate (138–414 nmol/l, 5.0–15.0 µg/dl) values we continue GC and retest the patients some weeks later. It is important to remember that if ACTH stimulation test is chosen for further assessment, at least 6 weeks from surgery should have passed to allow for adrenal atrophy to develop if ACTH secretion is abnormal. The standard (250 µg) and low (1 µg) dose ACTH stimulation tests have similar accuracy in the diagnosis of secondary AI,[19] with the latter not providing evident benefits 4–6 weeks after pituitary surgery.[20] Management of CD will be discussed below.

Disorders of water metabolism

Disruptions in water regulation can be linked to anatomic injury to the hypothalamus, pituitary stalk, or posterior pituitary gland during surgery. This damage alters the physiology of water metabolism controlled by the antidiuretic hormone (ADH) (see Figure 1).[21–24] These disorders of water metabolism can occur due to a decrease in ADH release, leading to central diabetes insipidus (DI), or excess ADH release leading to water retention and to the syndrome of inappropriate ADH secretion (SIADH). Very rarely, a cerebral salt-wasting syndrome (CSWS), an ADH-independent condition, can occur after pituitary surgery.

Central DI and SIADH

DI is defined as the concomitant presence of inappropriate hypotonic polyuria (urine output > 3 l/24 h and urine osmolality < 300 mOsm/kg) in the presence of high or normal serum sodium.[25] Other causes of postoperative polyuria should be considered, including intraoperative administration of large amounts of fluids, hyperglycemia caused or worsened by GC therapy, and, in acromegaly patients, a rapid drop in GH levels. The presence of both serum hyperosmolality and

hypernatremia is highly suggestive for DI, but these laboratory alterations can be absent if the patient is conscious and has free access to water.[26] Central DI can be transient or permanent, and partial or complete, depending on the kind and extent of the damage to hypothalamic magnocellular neurons. According to most case series, DI is the most common complication after pituitary surgery.[27] It occurs in approximately 10–30% of patients undergoing pituitary surgery, but it persists long term only in 2–7%,[4,28,29] with approximately 50% of patients remitting in 1 week and about 80% in 3 months.[30] The risk of permanent DI is higher in young patients, males, those with large intrasellar masses and postoperative CSF leak,[26,31] in those with a preoperative diagnosis of DI,[32,33] following surgery for craniopharyngioma or Rathke's cleft cysts,[34] and after repeated pituitary surgery (e.g. for CD).[29]

The onset of polyuria is usually abrupt, occurring within the first 12–24 h after surgery. Acute disorders of water metabolism can manifest in a triphasic pattern (in approximately 3% of patients): an initial polyuric phase, a subsequent antidiuretic phase (the patients can temporarily concentrate urine and SIADH and hyponatremia develops), and a final polyuric phase that is usually chronic.[35] Persistence of DI implies that at least 85–90% of hypothalamic magnocellular neurons have been damaged by surgery. Finally, the antidiuretic phase described above is sometimes isolated and represents SIADH. This temporary, late-onset (peaking 5–8 days after surgery) hyponatremia may be heightened by concomitant hypocortisolism as patients with unreplaced AI may also present with hyponatremia.[36] Figure 2 reports the pathophysiology management of the postoperative disorders of water metabolism.

To screen for potential development of postoperative DI and SIADH, we recommend measurement of urine output and fluid intake, urine specific gravity daily, and serum sodium every 6–12 h until discharge. For treatment of DI during the immediate postoperative period, we recommend as-needed use of short acting subcutaneous vasopressin (rather than desmopressin, DDAVP), with frequent reassessment of response and need to avoid administering an ADH when a SIADH phase is occurring. We favor the use of vasopressin at this stage because of its shorter duration of action, in case DI is transient and it reverts to SIADH. Hyponatremia usually develops between postoperative days 5–8,[2] and therefore these patients should routinely have a serum sodium level check approximately on postoperative day 6 or 7. Postoperative SIADH seems more frequent in patients with cardiac, renal or thyroid disease, older age and low body mass index, and in patients who receive a postoperative lumbar drain.[37]

Given its often transient course, it is important not to over-treat early postoperative DI, to reduce the risk of precipitating hyponatremia if the second SIADH phase were to occur. Finally, patients should be instructed to only drink to thirst, and periodically (every couple of weeks) stop their DI treatment during the 6 months after surgery to verify whether they still need it.

Mild (134–125 mmol/l) hyponatremia can be treated in outpatient setting with fluid restriction and frequent sodium checks, while more severe hyponatremia (<125 mmol/l) requires hospitalization with possible short-time use of hypertonic saline or ADH receptor antagonist drugs, being careful to avoid over-correction.[2]

CSWS

Very rarely, hyponatremia after pituitary surgery may be caused by CSWS, characterized by excessive natriuresis and extracellular volume depletion. While SIADH is characterized by euvolemic hyponatremia (and thus treated optimally by fluid restriction), CSWS is characterized by brain natriuretic peptide-mediated hypovolemic hyponatremia (and thus managed with hypertonic fluid administration). The differential diagnosis between SIADH and the rarer CSWS is sometimes difficult. Weight (increased/unchanged in SIADH and decreased in CSWS), serum osmolality (decreased in SIADH and increased/normal in CSWS), serum protein levels (normal/high in CSWS), and hematocrit (low/normal in SIADH and increased in CSWS) may help the differential diagnosis.[38]

Other possible complications

Apart from hypopituitarism and disorders of water metabolism, damage to parasellar structures can lead to other complications after pituitary surgery, including CSF leak, epistaxis, damage to the parasellar visual system, and damage to internal carotid arteries. Mortality rate for pituitary surgery in the USA is reported between

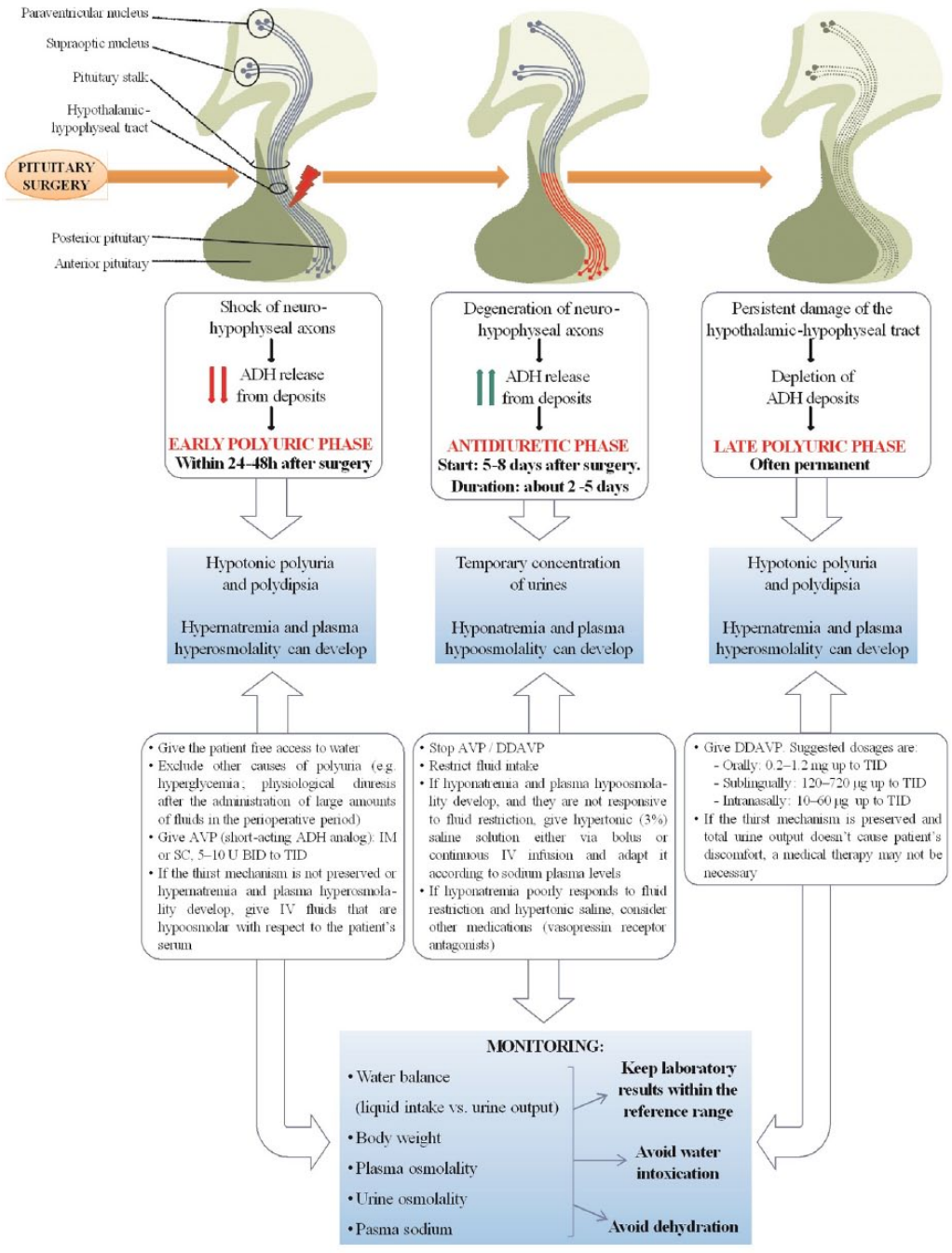

Figure 2. Pathophysiology and management of water metabolism imbalance after pituitary surgery.
bid, twice a day; ADH, antidiuretic hormone (vasopressin); AVP, arginine vasopressin; DDAVP, desmopressin; IM, intramuscular injection; SC, subcutaneous injection; SIADH, syndrome of inappropriate ADH secretion; tid, three times a day.

0.2–1.2%, with lower rates in neurosurgical units with more experience.[4,39]

A CSF leak usually manifests as rhino-liquorrhea and headache that is typically worse when sitting up and improves lining down. It may be associated with light sensitivity, nausea, and neck stiffness. CSF leak usually occurs in 0.5–4% of patients undergoing pituitary surgery,[4] although rates up to 40% have been reported.[40] A non-adenomatous disease, the need for surgical revision, tumor margins, size and increased consistency have been associated to the risk of intra and post-operative leaks.[41,42] CSF leaks have to be promptly

Table 3. Management of postoperative CSF leaks.

When to suspect?	How to confirm diagnosis?	Conservative treatments	Operative treatments
• Clear, watery nose discharge (usually unilateral) • The patient may refer salty or metallic taste • Headache may occur • If infectious meningitis develops other signs and symptoms appear (fever, severe headache, neck stiffness, confusion)	• Physical examination (including anterior rhinoscopy) • Test nose discharge for beta-trace or beta2-transferrin proteins • Cranial CT scans can help identifying the source of CSF leak	• Bed rest with head and torso tilt of 15–30° • Stool softeners to avoid increased intracranial pressure during bowel movements • Avoid actions that can lead to increased intracranial pressure (coughing, sneezing, nose blowing, heavy lifting) • Lumbar puncture and CSF drainage can be useful to reduce intracranial pressure. This procedure can sometimes block CSF leak • Some authors suggest giving antibiotic prophylaxis to prevent meningitis. However, there is currently no consensus	• Surgical repair. When the leak is revealed intraoperatively, it should be treated immediately, otherwise surgery *via* endoscopic technique should be planned as soon as the CSF leak is confirmed • Lumbar puncture and CSF drainage can help the postoperative course • If infectious meningitis develops treat with intravenous antibiotics and GC. • The most common bacteria causing ascending meningitis are *H. influenzae* and *S. pneumoniae*

ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency; CD, Cushing disease; CSF, cerebrospinal fluid; CT, computed tomography: GC, glucocorticoids; HPAA, hypothalamic–pituitary–adrenal axis.

recognized and treated, as they expose the patient to the risk of ascending infectious meningitis (Table 3).[43,44]

Loss of vision or ophthalmoparesis occur in approximately 0.5–2.5% of patients undergoing pituitary surgery in the USA.[4] They can be either caused by a direct surgical damage or by postoperative compression of optic structures by hemorrhage in the surgical bed. Delayed vision loss has been described as well, and it is generally attributed to herniation of the optic chiasm within the sella (secondary empty sella).[45]

Internal carotid artery injury is uncommon (0.5–1.5% of surgeries), but can lead to massive life-threatening bleeding.[4] Finally, postoperative venous thromboembolism can occur, especially in patients with CD, who harbor a higher thrombotic risk that persists for at least 3 months after surgery.[46] Therefore, postoperative thromboprophylaxis is advised by some authors in patients with CD although the optimal drug choice, dosing and durations are unknown.[47]

Special situations: CD management after primary surgery

After primary surgery for CD, the initial remission rate is between 25–100%.[29] Higher remission rates are observed for magnetic resonance imaging (MRI)-visible microadenomas without cavernous sinus invasion, and in centers where 36–40 patients were operated per year.[48] Nonetheless recurrent and persistent disease is a major issue, and second-line (and sometimes third-line) treatment options have to be considered, including repeated neurosurgery, radiotherapy, medical therapy, bilateral adrenalectomy, or a combination of these (Figures 3 and 4). The recurrence rate after neurosurgery is highly variable, ranging between 0–51.2% according to case series.[27,49,50] A recent meta-analysis places the risk of recurrence at 10%.[51]

How to establish CD remission after pituitary surgery?

If patients are not administered GCs, frequent (every 6 h) serum cortisol levels should be checked starting 12 h after completion of surgery. While typically serum cortisol nadirs 24–36 h after completion of surgery, cases of 'late cure' are reported.[52] We start GC therapy when serum cortisol drops below 138 nmol/l (5.0 μg/dl), or patients present symptoms of AI. The development of AI after pituitary surgery is the most immediate sign that neurosurgery has achieved a total or near-total resection of corticotroph tumor cells (see Table 2). Other biochemical tests can be used to confirm remission, and the most commonly used are report in Table 4.[29,53]

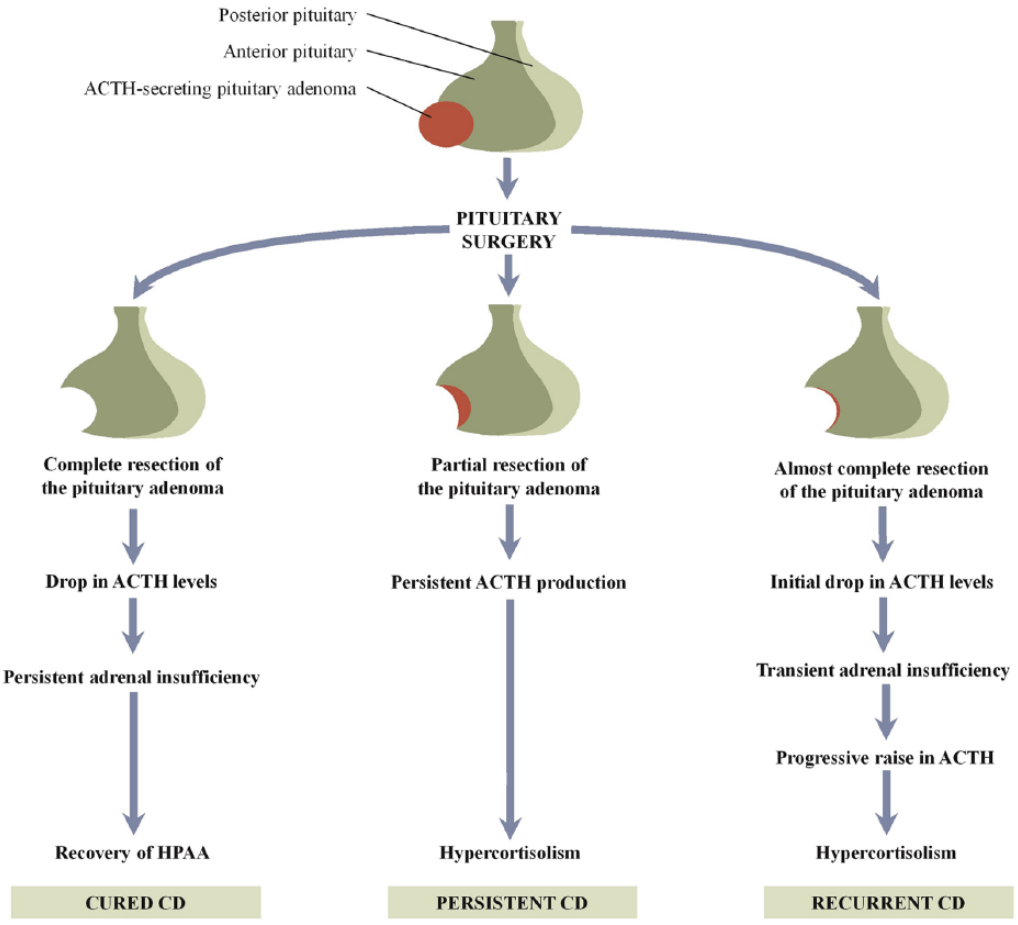

Figure 3. Cured, persistent and recurrent CD.
'Cured' CD means that the patient has gone into persistent remission, defined as normalization of the HPAA after surgery. 'Persistent' CD is defined as sustained hypercortisolism after pituitary surgery. The term 'recurrent' CD refers to hypercortisolism occurring after transient resolution (up to several years) of the abnormal cortisol secretion. Residual corticotroph tumor cells within the pituitary gland or surrounding structures are responsible for both persistent and recurrent CD.
ACTH, adrenocorticotropic hormone; CD, Cushing disease; HPAA, hypothalamic–pituitary–adrenal axis.

Morning serum cortisol is the most widely used tool to assess CD remission, although late-night salivary cortisol and DDAVP provocative testing have recently shown promising results.[54,55] Whatever test is used, it is worth noting that they lack reliable accuracy in predicting long-term CD remission. For example, 10% of patients with delayed relapse have very low postsurgical morning serum cortisol, and conversely, transient normal-to-elevated cortisol values in the immediate postoperative period are sometimes found in patients who will later go into persistent remission.[56] Therefore patients successfully treated for CD after pituitary surgery require lifelong follow up and retesting, according to clinical judgment.

Management of recurrent and persistent CD

The decision regarding the best treatment for recurrent and persistent CD is challenging. Several options are available, and the decision has to be tailored to each patient, taking into account the severity of symptoms, comorbidities, neuroimaging, surgical risks, desire for pregnancy, response and tolerance to medications.[57]

Surgical reintervention (when feasible) should be the first choice in cases of recurrent or persistent CD if postoperative MRI shows a clear, resectable tumor residue.[29,53] However, repeated surgery is characterized by lower success rate and a higher risk of complications (chiefly hypopituitarism, DI and CSF leaks) in comparison with primary

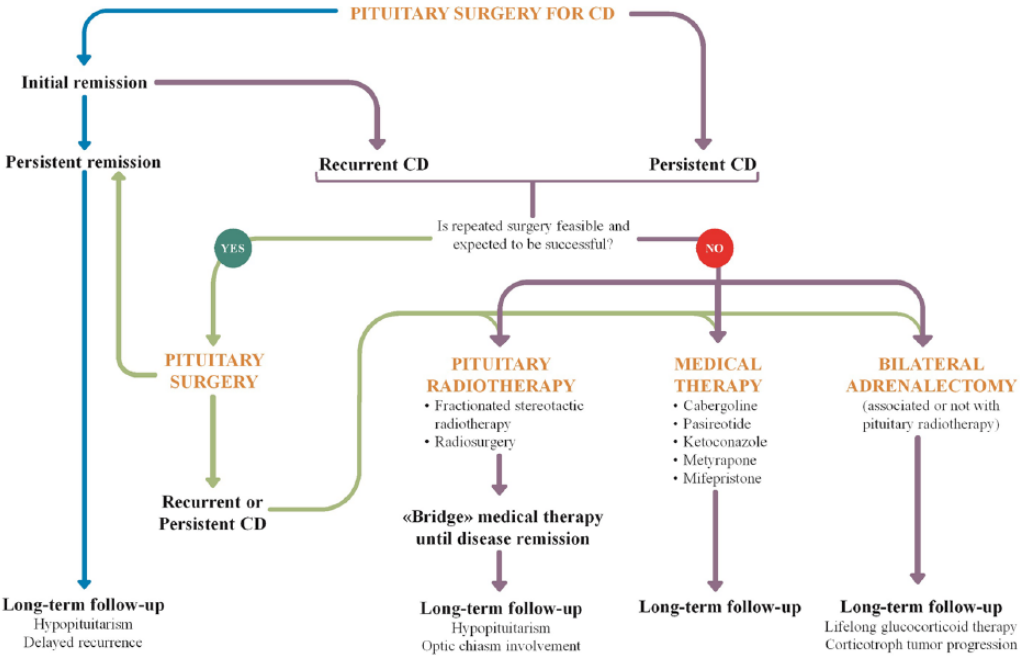

Figure 4. Management of patients with CD.
Possible scenarios during management of patients with CD. Lifelong follow up is mandatory for patients in persistent remission after first or repeated pituitary surgery, as they can develop disease relapse many years after surgical treatment. CD, Cushing disease.

Table 4. The most common ways to assess CD remission after neurosurgery.

Tool	Description
Postsurgical AI	Transient AI is expected after pituitary surgery (see Table 2). The longer duration of exogenous GC replacement, the better the long-term outcome
Postsurgical morning serum cortisol	• It is the most used test to assess remission after pituitary surgery • It is usually performed 1–7 days after surgery (before morning GC administration) • Remission is very likely for values <50 nmol/l (1.8 μg/dl) • Remission is likely for values <138 nmol/l (5 μg/dl) • Persistent disease is likely for values >200 nmol/l (7.2 μg/dl)
Late-night salivary cortisol	• Little but promising data • It is usually performed within the first days after surgery • Remission is likely for values <1.9 nmol/l (0.7 ng/dl) • Recurrence is likely for values >7.4 nmol/l (2.7 ng/dl)
DDAVP testing	• Little but promising data • It is usually performed within the first 6 months after surgery • 10 μg of DDAVP are given as IV bolus, with measurement of plasma ACTH and serum cortisol at 0, +15, +30, +45, +60, +90, and +120 min. A blunted response of ACTH (<50% over baseline) or cortisol (<20% over baseline) predicts remission

ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency; CD, Cushing disease; DDAVP, desmopressin; GC, glucocorticoids; IV, intravenous.

surgery. If reintervention is not a viable option or is expected to be unsuccessful (as judged by an experienced pituitary surgeon), second-line options (medical therapy, radiotherapy or bilateral adrenalectomy) have to be taken into account.

Special situations: acromegaly management after primary surgery

Similarly to CD, higher surgical remission rates in acromegaly are observed for microadenomas *versus* macroadenomas (particularly if extrasellar

extension in present), and in more experienced surgical hands.[58,59] Cure of acromegaly can cause significant diuresis, due to the drop of blood levels of GH and IGF-1 that cause fluid retention when inappropriately high.[60] This has to be taken into account in the differential diagnosis if postoperative polyuria develops.

Although early postoperative measurement of GH level can be a good predictor of cure, no obvious cut-off level has been identified.[61,62] Conversely, IGF-1 may take several months to normalize even in patients who are completely cured.[63] Serum GH and IGF-1 should be measured 12 weeks after surgery or later.[64] A postoperative 75 g oral glucose load showing GH $<$ 0.4 ng/ml within 2 h is currently considered the best test to assess remission in patients with abnormal IGF-1 or GH after pituitary surgery.[65]

Up to approximately 50% of acromegaly patients show persistence of the disease after pituitary surgery.[66] These patients require a multimodal approach to control GH excess, and possible strategies are repeated neurosurgery, medical therapy (somatostatin analogs, dopamine-receptor agonists, and GH-receptor antagonists), and radiotherapy.

Conclusion

The postoperative management of patients undergoing transsphenoidal pituitary surgery requires a multidisciplinary approach involving neurosurgeons, endocrinologists, and often intensive care teams. A preoperative hormonal assessment will help guide management decisions in the perioperative period, and intra and postoperative complications have to be promptly diagnosed and treated as to improve patient's outcomes and prognosis. Most complications resolve in the short term, but some persist and will require lifelong surveillance and treatment. In the light of such a multifaceted picture, we strongly suggest to refer patients requiring transsphenoidal surgery to tertiary centers where neurosurgeons, endocrinologists, and neurointensivists have the expertise to deal with these diseases.

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