



Postoperative management of patients with pituitary tumors submitted to pituitary surgery. Experience of a Spanish Pituitary Tumor Center of Excellence

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Abstract

There is a lack of evidence on timing, frequency, and duration of postoperative endocrine, radiologic, and ophthalmologic assessments that should be performed after pituitary surgery (PS). However, it is known that careful optimization of treatment and follow-up strategies as well as a multidisciplinary approach may have a significant impact on long-term outcomes, improving surgical results, minimize complications and facilitate their correct treatment if occurring, and optimize the hormonal, ophthalmological, and radiological reassessment throughout the follow-up. Considering that there are no specific guidelines on the postoperative management of patients with pituitary tumors (PT), we present our protocol for the postoperative management of patients with PT. It has been elaborated by the multidisciplinary team of a Spanish Pituitary Tumor Center of Excellence (PTCE) that includes at least one neurosurgeon, ENT, neuroradiologist, neuro-ophthalmologist, endocrine pathologist and endocrinologist specialized in pituitary diseases. We elaborated this guideline with the aim of sharing our experience with other centers involved in the management of PT thereby facilitating the postoperative management of patients submitted to PS.

Keywords Pituitary tumors · Pituitary surgery · Adrenal insufficiency · Glucocorticoid · Hypopituitarism · Diabetes insipidus

Introduction

Pituitary tumors (PT) are heterogeneous benign tumors of the central nervous system (CNS). They are present in up to 10% of the general population [1], but do not necessarily result into symptoms, either due to their small size or because they do not secrete hormones in excess. In

symptomatic cases, pituitary surgery (PS) by an expert neurosurgeon is usually the initial treatment of choice, with the exception of prolactinomas, in which medical treatment with dopamine agonists is preferred [2].

Nowadays, transsphenoidal surgery is the preferred surgical approach in more than 95% of the cases, even in PT with extensive suprasellar invasion or in some giant PT [3].

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Moreover, the transsphenoidal endoscopic approach (EEA) offers a better visualization of hidden structures, which are not usually visible under the direct microsurgical light [4–7].

The cure rate in the hands of expert pituitary surgeons ranges from 80 to 90% for microadenomas and from 40 to 70% for macroadenomas with a rate of major complications below 1% [8]. However, hyponatremia may occur in up to 10%, and hypopituitarism in 7.5% of patients submitted to experienced pituitary surgeons [9].

In the immediate postoperative period, the development of surgical and endocrine complications must be monitored and the need to continue with glucocorticoids (GC) replacement should be re-evaluated. The minimal setup includes monitoring of hydro-electrolyte balances and natremia, and active screening for potential development of surgical complications such as severe epistaxis, sellar hematoma, fistula of cerebrospinal fluid (CSF), etc. [10]. The omission of treatment with GC, desmopressin, and/or thyroid hormone when indicated leads to significant morbidity and mortality and must be avoided. In patients with acromegaly, Cushing's disease (CD) and prolactinomas, basal serum measurement of growth hormone (GH), cortisol and prolactin, respectively, on days 1–2 postoperatively has been shown to be predictive of early and long-term remission [11–15].

The late postoperative hormonal evaluation should be carried out 4–6 weeks after the intervention and aims to analyze the integrity of the pituitary function, with a special focus on the reevaluation of the corticotropic axis in the case of patients treated with GC. Pathology should be taken into account to plan long-term management since PT with histopathological features of aggressiveness should be followed up more closely [10, 16].

For the reasons outlined above, we truly believe that postoperative management of PT who are suitable candidates to PS optimally require a multidisciplinary team consisting of endocrinologists, neurosurgeons, ENT, neuro-ophthalmologists, neuroradiologists, and endocrine pathologists. The management of these patients in multidisciplinary specialized units with high-volume PT centers, especially in Pituitary Tumors Centers of Excellence (PTCE), provide the best care to patients with PT [17].

The present review based on our clinical practice protocol, recently updated according to available scientific evidence and published consensus of experts in pituitary pathology. We here describe in detail the structured protocol on the multidisciplinary management of patients undergoing PS due to PT, focusing on the postoperative study and management and on surgical treatment and its complications, with the aim of offering guidance to other multidisciplinary teams working in the field. The specific perioperative management of patients with CD and acromegaly is also briefly described.

Material and methods

The physicians involved in the management of patients with PT of Hospital Universitario Ramón y Cajal reviewed systematically current knowledge on the management of PT. The literature review used the online Entrez-PubMed facilities, including only publications in English and Spanish published from 1986 to 2019. More than 5000 papers were reviewed, of which only 85 were used to elaborate the postoperative protocol. The multidisciplinary team elaborated a first draft that was presented and perfected in a formal presentation with other doctors involved in the management of pituitary disease. The protocol was subsequently approved by the Hospital Quality Unit. This protocol is an update of that applied to the management of PT undergoing PS in our center during the last 5 years. Our hospital meets criteria to be considered a PTCE [17], having an experienced neurosurgeon with more than 300 endoscopic pituitary procedures performed, an average of 35–40 PS per year, and more than 330 outpatients under follow-up every year. The neurosurgery group works closely with endocrinologists on an endocrine unit that has a special emphasis on pituitary diseases with the aim of providing the best care for patients, and it is considered a training center for residents in the treatment of pituitary pathologies [17].

Description of our protocol for pituitary surgery

Intraoperative management

Surgical technique, outcomes, and complications

PT should ideally be performed in multidisciplinary specialized units with high-volume PT centers (PTCE) such as ours [17]. The experience of the surgical team is of paramount importance, facilitating long-term remission and gross total resection while minimizing complications [18–20]. Nowadays, the most commonly used approach is the transsphenoidal route either microsurgical (MA) or EEA [21]. We use EEA because, compared with the microscope, the endoscope offers the advantage of directly visualizing hidden areas that are not visible under the direct light of the microscope. Despite these theoretical advantages, the superiority of the EEA technique vs the classical MA technique cannot yet be clearly established. A comparison of the two techniques (micro and endoscopic) is limited because few studies are prospective or randomized. Therefore, it is based upon reviews and meta-analyses of studies of the individual techniques [22–32].

PS aims to eliminate excess hormone production (functioning PT (FPT)), avoid or ameliorate tumor mass effects, preserve both pituitary function and adjacent nerve

structures (optic and oculomotor nerves), and eliminate or reduce the risk of future recurrences [33]. The cure rate in the hands of expert surgeons is 80–90% for microadenomas and 40–70% for macroadenomas; with an overall rate of major complications (visual, CNS or carotid artery damage, CSF fistula and ophthalmoplegia) below 1% [8]. However, even with expert neurosurgeons, postoperative hyponatremia occurs in up to 10% of patients and hypopituitarism in up to 7.5% of PS [9] (Table 1). The cure rate in our center in the last 10 years is of 75% in acromegaly, 76% in Cushing disease, and the rate of major complications <5%.

Immediate postoperative cares

After PS is concluded, the patient will be transferred to the Intensive Care Unit (high-risk patients) or to the post-anesthesia care unit for regular surveillance during the first 12–24 h.

We consider the following as high-risk patients:

- Elderly patients (over 70 years).
- High comorbidity.
- Giant PT with cavernous sinus, III ventricle, or intracranial extension that needed expanded endoscopic approaches.
- Long-standing CD or acromegaly with serious comorbidities.
- Intraoperative major complications.

In the early postoperative phase, patients should be monitored for potential surgical (sellar hematoma, meningitis, CSF leakage, epistaxis) and endocrinological complications (diabetes insipidus (DI), hypopituitarism, SIADH). Nurses must check the patient for body temperature, blood pressure, conscience, rhinorrhea, and epistaxis every 8 h, and hydro-electrolytic balance at least daily, until discharge. If neurological symptoms or visual deterioration occurs, an urgent postoperative MRI or CT must be performed [34]. If rhinorrhea is suspected, beta-2 transferrin and beta trace protein test can be measured to confirm CSF leakage [35]. In case of relevant epistaxis, nasal package and reoperation should be done as soon as possible (Table 1).

Perioperative antibiotics should be maintained until removal of nasal packing and, in the absence of complications, the patient may be discharged the next day with home care recommendations (2–3 days after surgery).

Postoperative management of disorders of water metabolism

In the early postoperative period, the disorders of water metabolism are common yet often transient complications.

These disorders include DI, SIADH and, although very infrequent, the cerebral salt-wasting syndrome (CSWS).

Central diabetes insipidus and SIADH

Postoperative DI can be transient or permanent and partial or complete, depending on the type and extent of the damage to hypothalamic magnocellular neurons. DI is one of the most common complications after PS [36]. It occurs in ~10–30% of patients undergoing PS, but long-term persistence only happens in 2–7% of cases [18, 37, 38]. The risk of permanent DI is higher in young patients, men, large intrasellar masses, and postoperative CSF leakage [39, 40], patients with a preoperative diagnosis of DI [41, 42], following surgery for Rathke's cleft cysts or craniopharyngioma [43], and after repeated PS [37]. Because GC are necessary for the excretion of water overload, DI may become first apparent when a patient with secondary adrenal insufficiency (SAI) starts GC therapy. Moreover, other causes of postoperative polyuria, including intraoperative administration of large amounts of fluids, hyperglycemia caused or worsened by GC therapy, and a rapid decrease in GH levels in acromegaly should be ruled out. The presence of serum hyperosmolality and hypernatremia is highly suggestive of DI, but these alterations may be absent in patients in whom water intake is not restricted [44].

DI can appear at any time but usually manifests as the sudden onset of polyuria, accompanied by thirst and polydipsia, within the first 48 h after PS. In most patients, vasopressin secretion recovers, and DI is usually transient, resolving gradually over a period of 3–5 days.

In ~3% of patients, acute postoperative water balance disorders follow a three-phase pattern consisting of an initial polyuric phase (DI) followed by an antidiuretic phase (SIADH) caused by the release of stored vasopressin and a final polyuric phase (DI) that translate depletion of hormone reserves and is usually permanent [39, 45]. Finally, the antidiuretic phase described above is sometimes isolated and represents SIADH. This late-onset of transient hyponatremia can increase due to concomitant hypocortisolism, since patients with untreated adrenal insufficiency may also associate hyponatremia [46].

To screen patients for the potential development of postoperative DI and SIADH, we measure urine output and fluid intake, as well as serum sodium, on a daily basis until discharge (Table 3). Desmopressin is used for DI during the immediate postoperative period, with frequent reassessment of its requirements. Given the frequent transient course, it is important to avoid overtreatment of early postoperative DI in order to reduce the risk of precipitating hyponatremia if followed by a SIADH phase.

Table 1 Diagnosis and management of postsurgical complications

	Diagnosis	Management
Postoperative hormonal complications		
Central diabetes insipidus	<p>Criteria for the diagnosis of postoperative DI:</p> <ul style="list-style-type: none"> • Diuresis >3 L/d or >50 mL/kg/d • Serum Na >145 mmol/L and serum osmolality >295 mOsm/kg (could be normal if the thirst mechanism is intact) • Urine osmolality <300 mOsm/kg <p>Comments:</p> <ul style="list-style-type: none"> • Measure simultaneously serum and urine osmolality in patients with polyuria • DI may appear when a patient with SAI starts GC • Rule out other causes of postoperative polyuria: intraoperative administration of large amounts of fluids, hyperglycemia, rapid decrease of GH in acromegaly • Serum Na <135 mmol/L and plasma osmolality <275 mOsm/kg • Clinical euvolesmia (if hypovolemia consider CSWS). • Urine osmolality >100 mOsm/kg • Urine Na concentration >40 mmol/L with normal dietary salt and water intake <p>Comments:</p> <ul style="list-style-type: none"> • Rule out hypothyroidism, renal and adrenal insufficiency, or recent use of diuretics 	<p>Desmopressin (DDAVP)</p> <ul style="list-style-type: none"> • Oral: 0.1 mg/12–24 h (tablets) • Sublingual: 60 mcg/12–24 h • If the oral route is not possible: subcutaneous or intravenous 1–2 µg/12–24 h <p>Monitoring: fluid intake, diuresis, and serum Na levels to avoid hyponatremia. Adjust dose according to clinical criteria (daily diuresis, presence or absence of nicturia)</p> <p>Comments:</p> <p>At least one attempt to discontinue DDAVP during the weeks or months following PS is needed to analyze the possible recovery of posterior pituitary function</p> <ul style="list-style-type: none"> • Water restriction: 500–1000 mL/d • Increase NaCl intake to a minimum of 5 g/d • Second-line treatments: 0.25–0.50 g/kg per day of urea or a combination of low-dose loop diuretics and oral NaCl • In severe cases (serum Na <120 mmol/L) use intravenous infusion of hypertonic saline <p>Comments:</p> <ul style="list-style-type: none"> • Home monitoring of fluid intake and urine output after discharge • Measurement of serum Na weekly after surgery or urgently if symptoms of hyponatremia • Avoid water restriction • Intravenous isotonic saline solution in sufficient quantity to induce positive sodium balance • In severe cases (serum Na <120 mmol/L) use hypertonic saline solution and continue with isotonic saline solution when serum Na is >120 mmol/L <p>Comments:</p> <ul style="list-style-type: none"> • Fludrocortisone should be used only if fluids and salt replacement cannot counteract excess natriuresis
Cerebral salt-wasting syndrome (CSWS)	<ul style="list-style-type: none"> • Serum Na <135 mmol/L and plasma osmolality <275 mOsm/kg • Clinical hypovolemia (e.g., hypotension, poor skin turgor, elevated hematocrit, etc.) • Diuresis >3 L/d • Urinary Na >40 mmol/L <p>Comments:</p> <ul style="list-style-type: none"> • A very high urine Na concentration, high serum urea, orthostatic hypotension, and a low central venous pressure argue in favor of CSWS • The main difference with SIADH is that excessive natriuresis leads to a reduced extracellular volume 	<ul style="list-style-type: none"> • Avoid water restriction • Intravenous isotonic saline solution in sufficient quantity to induce positive sodium balance • In severe cases (serum Na <120 mmol/L) use hypertonic saline solution and continue with isotonic saline solution when serum Na is >120 mmol/L <p>Comments:</p> <ul style="list-style-type: none"> • Fludrocortisone should be used only if fluids and salt replacement cannot counteract excess natriuresis
Postoperative surgical complications		
CSF leakage	<p>Confirmation: Beta-trace or beta 2 transferrin</p> <p>Comments:</p> <ul style="list-style-type: none"> • β-trace values ≥ 1.3 mg/L indicate the presence of CSF in secretion. β-trace between 0.7–1.29 mg/L indicate the presence of CSF if the β-trace ratio (β-trace secretion/β-trace serum) is ≥ 2 • Emergency MRI o CT scan 	<ul style="list-style-type: none"> • Surgical closure (nasoseptal flap or the multilevel closure with artificial materials) as soon as possible <p>Comments:</p> <ul style="list-style-type: none"> • CSF leak can be prevented if the arachnoid membrane is not traumatized
Sellar/hematoma	<p>Comments:</p> <ul style="list-style-type: none"> • Postoperative sellar hematoma is a rare phenomenon after transsphenoidal surgery, often presenting with visual loss and headache <p>The diagnosis is clinical</p> <p>Comments:</p> <ul style="list-style-type: none"> • The initial evaluation of epistaxis should focus on airway assessment and cardiovascular stability 	<ul style="list-style-type: none"> • Surgical decompression as soon as possible <p>Comments:</p> <ul style="list-style-type: none"> • Close postoperative scrutiny should be given to patients at high risk as a preventive measure • Aggressive nasal packing, stabilization in ICU, angiogram \pm surgical re-exploration <p>Comments:</p> <ul style="list-style-type: none"> • When massive delayed nasal bleeding follows PS and damage of the internal carotid artery has been ruled out, endovascular treatment of the external carotid artery should be considered
Massive epistaxis		

Table 1 (continued)

Postoperative hormonal complications	
Diagnosis	Management
<p>Meningitis</p> <ul style="list-style-type: none"> • Confirmation: Lumbar puncture • Comments: <ul style="list-style-type: none"> • Characteristic findings in bacterial meningitis include a CSF glucose concentration <40 mg/dL, a CSF to serum glucose ratio of <0.4, a protein concentration >200 mg/dL, and a white blood cell count above 1000/mcL, usually composed primarily of neutrophils • Postoperative CSF leakage is an important risk factor for meningitis after PS. • The incidence is higher in macroadenoma than microadenoma 	<ul style="list-style-type: none"> • Antibiotic intravenously for 14 days • Comments: <ul style="list-style-type: none"> • Systemic, early and empirical antibiotic therapy should be initiated if there are clinical suspicions, without waiting for the results of the antibiogram

DI diabetes insipidus, *SAI* secondary adrenal insufficiency, *GC* glucocorticoids, *PS* pituitary surgery, *CSF* cerebrospinal fluid, *ICU* intensive care unit

Hyponatremia usually develops between postoperative days 5 and 8 [34] and, therefore, PS patients should undergo serum sodium measurements on postoperative days 5–7. The incidence of postoperative hyponatremia appears to be higher in patients with cardiac, renal, and/or thyroid disease, in females, and in patients suffering postoperative CSF drainage [47]. Mild-moderate hyponatremia (134–125 mmol/L) may be treated at the outpatient setting with fluid restriction and frequent circulating sodium controls, whereas more severe hyponatremia (<125 mmol/L) requires hospitalization and the possible use of intravenous infusion of hypertonic saline [48]. On the other hand, a recent study proposes that the prevention of the development of postoperative hyponatremia is possible with 1.0 L daily fluid restriction. They found that in the intervention group none was readmitted for hyponatremia (0/203), compared with 3.41% (20/585) in the control group ($p = 0.003$) [49]. Our recommendations for treatment are summarized in Table 1.

Cerebral salt-wasting syndrome

Very rarely, postoperative hyponatremia results from CSWS, a disorder characterized by excessive natriuresis and decreased extracellular volume. As opposed to the euvolemic hyponatremia of SIADH, CSWS is characterized by hypovolemic hyponatremia and necessarily requires volume replacement for recovery. Fludrocortisone should be used only if sodium and fluid replacement is unable to counteract excessive natriuresis [50]. The differential diagnosis between SIADH and CSWS is sometimes difficult. Table 2 summarizes the most important characteristics and differences between these two entities [51, 52].

Postoperative reassessment

In the late postoperative period, we reassess the adrenal, thyroid, gonadal, and somatotrophic axes. Long term monitoring of visual and pituitary function, coupled with pituitary imaging (preferably MRI) and ENT evaluation, is necessary for all patients who underwent PS.

Postoperative hormonal evaluation

One of the most common complications after PS is hypopituitarism [53], which can be partial or total, and transient or permanent. The hormonal assessment and the management of anterior pituitary hormone deficiencies after PS is summarized in Table 3.

The risk of hypopituitarism after PS varies according to the etiology, ranging from 5–25% in PT to as much as 76% in craniopharyngiomas [54], with its occurrence largely depending on the neurosurgeon's experience [18, 55]. Other

Table 2 Characteristics and differences between CSWS and SIADH

	CSWS	SIADH
Intravascular volume	↓	Normal or ↑
Clinical data of dehydration	Present	Absent
Central venous pressure	↓	Normal or ↑
Serum sodium	↓	↓
Urinary sodium	↑↑	↑
Serum osmolality	↓	↓
Urinary osmolality	↑	↑
Urine volume	↑↑	Normal or ↓
Sodium balance	Negative	Variable
Water balance	Negative	Normal or ↑
Plasma BUN/creatinine	Normal or ↑	Normal or ↓
Vasopressin level	↓	↑
Treatment	Sodium and volume replacement. Mineralocorticoids	Fluid restriction

BUN blood urea nitrogen, *CSWS* cerebral salt-wasting syndrome, *SIADH* syndrome of inappropriate ADH secretion

factors, including the size and consistency of the tumor, the extent of the resection, and surgery for recurrent disease, increase the chances of hypopituitarism [18].

Provided that no acute complications have occurred in the immediate postoperative period, we performed the first evaluation of anterior pituitary function 4–6 weeks after surgery (Table 3).

Postoperative imaging evaluation

In most hospitals, including ours, early postsurgical imaging studies are not performed. Unless the occurrence of surgical complications, pituitary imaging should be delayed for 3 to 6 months after surgery, because anatomical changes resulting from surgical manipulation may lead to erroneous interpretation of the findings [56]. To facilitate comparison, postoperative imaging procedures should follow the protocols used before PS.

In the case of complications, imaging studies should be performed immediately. In addition to the usual MRI protocols, the use of GREpT2* sequences (hemorrhages) and MRI-angiography (vascular lesions), as well as even invasive tests such as angiography, may be necessary. In actual emergencies, the usually more accessible brain CT may suffice to diagnose severe complications [56].

• Microadenomas protocol

1. T1wSE sagittal 2.5–3 mm without intravenous contrast
2. 2.5–3 mm coronal T1wSE without intravenous contrast
3. T2wTSE coronal 2.5–3 mm without intravenous contrast
4. Intravenous post contrast coronal dynamic series
5. T1wSE coronal 2.5–3 mm post intravenous contrast
6. T1wSE sagittal 2.5–3 mm post intravenous contrast

• Macroadenomas protocol

1. T1wSE sagittal 2.5–3 mm without intravenous contrast
2. 2.5–3 mm coronal T1wSE without intravenous contrast
3. T2wTSE coronal 2.5–3 mm without intravenous contrast
4. T1wSE coronal 2.5–3 mm post intravenous contrast
5. T1wSE sagittal 2.5–3 mm post intravenous contrast

Postoperative neuroophthalmological evaluation

In our center, postoperative assessment includes visual acuity (VA), pupil and ocular motility, fundus examination, visual field (VF) testing and optical coherence tomography (OCT).

Resection of PT improves visual function in up to 80–90% of patients [57]. VA recovers rapidly after surgical decompression and further improvements may continue over the next few months. According to Kerrison [58], VF improvement follows a triphasic manner—translating release of the conduction block, re-myelination, and neuronal plasticity—and takes months to years to recover.

Postoperative visual improvement may be observed even in patients presenting with pituitary apoplexy. Rates of improvement of VA, VF defect, and ocular palsy of 92.9%, 94.7%, and 100% have been recently reported, with full VA, VF, and ocular palsy recovery being observed in 57.1%, 36.8% and 96.4% of cases, respectively [59].

Although there are no guidelines for long-term follow-up, we suggest an initial postoperative visit at 3 months followed by examinations every 6 months until visual function stabilizes, followed by annual monitoring [60].

Postoperative ENT evaluation

The removal of the nasal tamponade and a nasal endoscopy to assess the state of the surgical site are recommended 48–72 h after surgery. Three weeks later, we remove the silastic plates left from PS, to avoid nasal synechiae and an endoscopic revision is repeated.

Table 3 Evaluation after pituitary surgery

	Diagnosis	Treatment and monitoring
(1) Postoperative hormonal evaluation Secondary AI Central hypothyroidism Central hypogonadism	<p>Re-test for HPAA function 4–6 weeks after surgery:</p> <p>1. Screening: Morning serum cortisol (>24 h after the last HC dose or longer for synthetic GC). Same cut-offs as those used preoperatively (see Table 1).</p> <p>2. Confirmation (provocative tests):</p> <ul style="list-style-type: none"> • IIT: 'gold standard' to assess HPAA recovery. <p>Contraindications: elderly patients and cardiovascular, cerebrovascular, or seizure disorders.</p> <ul style="list-style-type: none"> • ACTH stimulation test for cortisol (250 or 1 µg): the most widely used test. <p>Comments:</p> <ul style="list-style-type: none"> • The ACTH stimulation test can be unreliable in partial SAI after recent PS (<1 month). If a provocative test is needed and IIT is contraindicated, the patient should be kept on replacement therapy and an ACTH stimulation test can be planned later during follow up. • Patient not placed on GC in the postoperative period: instruct the patient to monitor any signs and symptoms of AI in the immediate days following discharge and re-test HPAA function 4–6 weeks after surgery. • Patients with SAI before PS: the probability of HPAA recovery after surgery is very low and the need for lifelong GC replacement therapy is quite likely. A single postoperative morning serum cortisol before taking the first dose of GC may be enough to confirm persistent AI. <p>Serum TSH and FT4:</p> <ul style="list-style-type: none"> • A FT4 level below the laboratory reference range with a low, normal, or mildly elevated TSH usually confirms the diagnosis. <p>Serum LH, FSH, total testosterone (in men), and estradiol (in premenopausal women).</p> <p>In men second testosterone measurement may be needed, and free testosterone and SHBG may be performed in selected cases, for confirmation.</p> <p>Comments:</p> <ul style="list-style-type: none"> • Exclude other causes of menstrual irregularities related to impaired ovulation: hyperprolactinemia, hyperandrogenism, and thyroid disease. • In cases of amenorrhea: exclude pregnancy. • Normal menses in a premenopausal woman rule out hypogonadism. • In postmenopausal women, the absence of high serum FSH and LH is 	<p>Hydrocortisone:</p> <p>15–20 mg total daily dose in single or divided doses.</p> <p>OR</p> <p>Modified-release HC: 20–30 mg orally once daily.</p> <p>Monitoring:</p> <ul style="list-style-type: none"> • Body weight, blood pressure and quality of life. • ACTH is not useful during the follow up of SAI. <p>Comments:</p> <ul style="list-style-type: none"> • Exclude AI before starting levothyroxine or rhGH to prevent adrenal crisis: levothyroxine enhances the clearance of cortisol and GH blocks the conversion of cortisone to cortisol. • Treating AI may unmask central DI. • Instruct the patients and their caregivers to increase the dose of GC in case of stressful events and to recognize an adrenal crisis, which requires immediate administration of parenteral fluids and HC. <p>Levothyroxine sodium:</p> <ul style="list-style-type: none"> • Appropriate levothyroxine doses average 1.6 µg/kg/d, with dose adjustments based on clinical context, age, and serum FT4 levels. <p>Serum TSH is not useful during the follow up of central hypothyroidism.</p> <p>Comments:</p> <ul style="list-style-type: none"> • Exclude SAI before starting levothyroxine. • rhGH can reduce levothyroxine and, therefore, can unmask central hypothyroidism or lead to higher levothyroxine requirements • Oral estrogens may increase thyroid binding globulin increasing replacement doses of levothyroxine. <p>When the patient is not interested in fertility:</p> <ul style="list-style-type: none"> • Testosterone (males): <p>Monitoring: Serum total testosterone, PSA and hematocrit.</p> <ul style="list-style-type: none"> • Estrogens + progestins if the patient has an intact uterus (females): <p>Monitoring: The presence of normal menses indicates adequate estrogenic replacement therapy.</p> <p>When the patient wants to become fertile:</p> <ul style="list-style-type: none"> • Gonadotropins. <p>Comments:</p> <ul style="list-style-type: none"> • In women under GH therapy transdermal estrogen formulations are preferred, if possible, as the oral route reduces peripheral sensitivity to GH.

Table 3 (continued)

	Diagnosis	Treatment and monitoring
GH deficiency	<p>sufficient for the diagnosis (provided the patient is not on hormonal replacement therapy).</p> <p>Screening:</p> <ul style="list-style-type: none"> • Serum IGF-1 <p>Confirmation:</p> <p>Use one or more among:</p> <ul style="list-style-type: none"> • IIT for GH (GH <3 ng/ml) • Glucagon stimulation test (GH <3 ng/ml) • GHRH + arginine stimulation test (GH <4 ng/ml) <p>Comments:</p> <ul style="list-style-type: none"> • Cutoffs for GH response should be correlated to BMI. • GHRH + arginine stimulation test can give false normal GH response if GHD is due to hypothalamic damage (eg, after radiation). • In patients with multiple pituitary hormone deficiencies after surgery (3 or more axes affected) GH deficiency is very likely to be present, and in this context provocative testing is optional. • Exclude hypothyroidism, since it induces blunted responses to dynamic tests. <p>(2) Postoperative radiological evaluation</p> <ul style="list-style-type: none"> • Perform between 3 and 6 months after surgery. • Same protocols as used preoperatively. • In case of complications: GREpT2* sequences (hemorrhages) and MRI-angiography (vascular lesions), and even invasive tests, such as angiography, may be necessary. Consider CT in urgent complications. <p>(3) Postoperative ophthalmological evaluation</p> <ul style="list-style-type: none"> • VA, pupil and ocular motility, fundus examination, VF testing and OCT. • Visual improves in up to 80–90% of patients. • VA recovers rapidly after surgical decompression and improvement can continue over the next few months. • In patients with pituitary apoplexy: rates of VA, VF defect, and ocular palsy improvement of 92.9%, 94.7%, and 100% respectively have been recently reported. • Postoperative visit at 3 months and then every 6 months until the visual function stabilizes, followed by annual monitoring. <p>(4) Postoperative ent evaluation</p> <ul style="list-style-type: none"> • It is performed 48–72 h after surgery. • Same tests as preoperatively. 	<ul style="list-style-type: none"> • CD can cause hypogonadism per se. Therefore, as the effects of previous hypercortisolism can be long-term, biochemical assessment for central hypogonadism should not be performed before several months since successful PS. <p>rhGH:</p> <ul style="list-style-type: none"> • Starting dose: <ul style="list-style-type: none"> • 0.2–0.4 mg/d for patients younger than 60 years • 0.1–0.2 mg/d for patients older than 60 years. <p>Monitoring: Titrate GH doses to maintain IGF-1 levels below the upper limit of normal of the age-adjusted reference ranges. Other important parameters of control include quality of life, body weight and composition, waist circumference, blood pressure and metabolic profile. Reduce the dose if side effects manifest.</p> <p>Comments:</p> <ul style="list-style-type: none"> • Women usually require higher doses than men. • Women on oral estrogens have higher rhGH requirements (consider switching to transdermal formulations).
	<p>AI adrenal insufficiency, BMI body mass index, CD Cushing disease, DI diabetes insipidus, GC glucocorticoids, GHD GH deficiency, GHRH growth-hormone-releasing hormone, HPAA hypothalamic–pituitary–adrenal axis, IGF-1 insulin-like growth factor type 1, LH luteinizing hormone, rhGH recombinant human growth hormone, SHBG sex hormone-binding globulin, IIT insulin tolerance test, PS pituitary surgery, HC hydrocortisone</p>	

Nasal complications and sequelae have little clinical expression and are considered minor complications [61]. Smell disorders are not frequent except in cases of involvement of the cribriform plate [62]. To assess the nasal status and the anatomical and functional repercussion of the PS approach, the tests that were performed preoperatively are repeated at 3 and 6 months after surgery, including endoscopy, visual analogic scales of obstruction, rhinorrhea, facial pain and anosmia, functional tests, SNOT 22 questionnaire, and smell test.

Assessment of pathology reports

Fresh pituitary specimens should be submitted to Pathology immediately upon removal from the patient. Diagnostic material is fixed in formalin and nonessential tissue for diagnosis is processed for biobank storage under pathologist's supervision. Of note, adequate fixation is crucial for histological and immunohistochemical assessment. The most important prognostic factor that pathologists can provide is an accurate diagnosis.

We use the current World Health Organisation (WHO) classification of pituitary neuroendocrine tumors (PitNET) [63]. This classification relies on the expression of pituitary-specific transcription factors such as Pituitary transcription factor 1 (Pit-1), T-box family member TBX19 and steroidogenic factor 1, and anterior pituitary hormones, as assessed by immunohistochemistry. The main advantage of this classification is the concordance with patients' clinical course and prognosis [64]. Sparsely granulated silent somatotroph adenomas are associated with a poor response to somatostatin analogs. Densely granulated lactotroph adenomas, silent corticotroph adenomas, Crooke cell adenomas, and plurihormonal poorly differentiated Pit-1 positive adenomas are associated with more aggressive features and a higher risk of relapse. A Ki67 proliferation index above 3% or the presence of more than 2 mitoses per 10 microscopic high-power fields are also associated with a higher risk of relapse [64–66]. On the contrary, the prognostic value of p53 expression is unclear at present [64]. Other prognostic markers that are currently under study and may be useful in the near future are estrogen receptor alpha, E-cadherin, O6-methylguanine DNA methyltransferase, and aryl hydrocarbon receptor interacting protein (AIP) [67].

Pathology also served for the differential diagnosis of other pathologies and tumors originated in the pituitary gland and of metastatic disease, especially in the context of silent tumors. In our usual clinical practice, we generally do not guide postsurgical treatment based on the pathology report, but we use this information to plan follow-up: in those PT with data suggesting a more aggressive behavior we perform a closer follow-up consisting of visits every 3–6 months (depending on the growth rate and proximity to vital structures) for at least 2–3 years, and subsequently

annual visits if tumor stability is confirmed by both hormonal and imaging tests [68].

Special cases

Postoperative long-term follow up varies depending on the diagnosis and is most challenging in patients with CD and acromegaly, in whom failure of PS is a major concern.

Cushing's disease

Patients with CD must receive steroid coverage according to the usual the schedule. Usually, they are treated with hydrocortisone replacement doses at discharge until the hipotalamic pituitary adrenal axis (HPAA) is re-evaluated to assess cure or persistence of cortisol excess.

Successful tumor resection leads to GC deficiency due to the presumed inhibition of ACTH secretion from the remaining normal corticotrophic cells by long-standing exposure to hypercortisolism. Hence, postoperative endogenous hypocortisolism is indicative of surgical success [69–71]. However, suppression of endogenous ACTH secretion by normal corticotrophs may not happen in patients under medical therapy in whom eucortisolism was attained preoperatively or in those with mild or cyclic preoperative hypercortisolism, leading to normal cortisol levels after total tumor resection. Such patients may not require additional GC therapy, and the tests used for the initial diagnosis of Cushing's syndrome must be performed to confirm remission accurately. Hypocortisolism and GC withdrawal symptoms should be monitored in all patients and managed with physiological GC replacement doses until the HPAA is fully recovered, a milestone that might require years in some cases.

Nowadays there is no universal consensus on the criteria that should be used to establish or predict cure of CD after PS [72–77]. Several methods have been used: (1) non-provocative tests including the measurement of morning serum cortisol and/or plasma ACTH levels and/or daily urinary free cortisol (UFC) levels during the immediate postsurgical period; and (2) provocative tests including the overnight or 2-day low-dose dexamethasone suppression test (DST), the CRH stimulation test, and the desmopressin stimulation test within the 3 months after surgery. Nowadays the most used cure criteria in the immediate postoperative period are those also employed in our center, as follows [73]:

- Morning serum cortisol <1.8 µg/dL (higher long-term remission rates, 85–100% [11–13]).
- Normal UFC.

Although extremely low serum cortisol (<1.8 µg/dL) is the best predictor of cure, some patients with low but detectable

Fig. 1 Calendar of medical visits after pituitary surgery

NEUROSURGERY CONSULTATIONS	ENDOCRINOLOGY CONSULTATIONS	ENT CONSULTATIONS	OFTALMOLOGY CONSULTATIONS
<ul style="list-style-type: none"> • (1 month - 6 months - 1 year - annual / biannual) • Order the Post-PS MRI (4-6 months post-PS) 	<ul style="list-style-type: none"> • (1 month - 3 / 6 months - 1 year - every 6 months / 1 year) • Basal control hormonal study. 	<ul style="list-style-type: none"> • (15 days - 2/3 months - 6 months -year) • Endoscopy and silastic withdrawal. 	<ul style="list-style-type: none"> • (3 months - every 6 months) • In case of previous visual affection or post-PS • VA, FT, OCT and post-PS VF test

PS= pituitary surgery; VA= visual acuity; FO; FT= fundus test; OCT= optical coherence tomography; VF= visual field

concentrations (2–4 µg/dL) that suppress with low-DST may remain in long-term remission [71]. A less stringent post-operative criterion is based on a postoperative serum cortisol concentration <5 µg/dL within 14 days of surgery, which associates initial cure rates of up to 80–90% after transsphenoidal microadenectomy in some studies [78–81], but long-term remission rates between 65 and 80% in others [81, 82]. Occasionally, some patients appear to have a late remission and the serum cortisol levels decline more gradually [83], possibly indicating the progressive necrosis of remaining tumor cells. Thus, it is important to ensure that cortisol has reached the lowest level before considering additional therapy. Measurement of UFC can provide additional useful information when the serum cortisol level is equivocal. The urine collection should begin at least 24 h after the last dose of hydrocortisone; a small maintenance dose (0.25–0.5 mg) of dexamethasone may be substituted instead of hydrocortisone before and during the collection. Levels above normal range indicate tumor persistence [72, 84, 85].

In our center, we measure serum cortisol and UFC in the immediate postoperative period before discharge (day 4–5 after surgery) for the evaluation of remission. Patients with basal serum cortisol <1.8 mcg/dl and normal UFC are considered cured. In patients with postsurgical eucortisolism, we perform two serum cortisol measurements in the morning within the first 2 weeks after surgery, with exogenous hydrocortisone withdrawal of at least 24 h before the first cortisol measurement. In patients in whom it is not possible to measure cortisol in the absence of steroid treatment within the 2 weeks after surgery, the assessment of the HPA axis is performed in outpatient setting 4–6 weeks after discharge. If there is a reason to suspect tumor persistence, we perform a late-night salivary cortisol measurement as well as the DST. For persistent endogenous hypercortisolism (high UFC), we consider additional therapy (medical treatment, repeated PS, and/or radiotherapy). Patients with normal cortisol dynamics, in whom normal corticotroph cells may not be suppressed, are carefully monitored.

In patients who fully met criteria for remission, hydrocortisone replacement doses should be administered until complete recovery of the HPA axis, a process that may take months or even years). The management of patients with intermediate postoperative values of cortisol should be

individualized. All patients should be re-evaluated at least annually for several years and less frequently thereafter, and they should be advised to consider reassessment at any time if they experience a recurrence of their previous symptoms.

Acromegaly

In patients with GH-secreting PT, random IGF-1, and GH concentrations should be measured 12 weeks after surgery.

The postsurgical remission criteria that we use are:

- IGF-1 within the normal range adjusted for age and sex; and
- GH <0.14 ng/ml.

GH levels <0.14 ng/ml suggest “surgical remission”, whereas GH levels <1 ng/ml indicate “control” and normalization of mortality risk [14, 15]. In those patients presenting with IGF-1 above the age- and sex-adjusted normal range, or those with baseline GH >1 ng/ml, serum GH levels should be measured during an 75 g oral glucose tolerance test (OGTT) [14]. A normal response is based on a GH during the OGTT <1 ng/ml (or <0.4 ng/ml with ultra-sensitive assays as ours).

In patients with persistent disease after surgery, an individualized treatment strategy based on medical therapy, repeated PS, and/or radiotherapy should be considered.

Long-term follow up by the different specialists

Data from all patients undergoing PS are included in a database designed for this purpose after giving appropriate written informed consent. This register follows all recommendations of local and European data protection law and has been approved by the local ethics committee.

In usual conditions, outpatient follow-up visits in Neurosurgery and Endocrinology are carried out 1, 6, and 12 months after PS, and then at an annual basis. This schedule may be modified according to the specific characteristics of each case. In addition, they are followed-up at the outpatient Rhinology facilities at least during the first postsurgical year (Fig. 1).

Conclusions

The optimal postoperative management of PT submitted to PS requires a multidisciplinary approach involving a team of endocrinologists, neurosurgeons, ENT, neuro-ophthalmologists, neuroradiologists, and pathologists with experience in pituitary diseases. Such teams improve surgical results, minimize complications and facilitate their correct treatment if occurring, and optimize the hormonal, ophthalmological, and radiological reassessment throughout the follow-up. Through this multidisciplinary protocol on postoperative management of PT, currently in use at a PTCE, we aimed to share our experience with other centers that treat these patients, in order to facilitate the management of patients undergoing PS.

Conflict of interest The authors declare that they have no conflict of interest.

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