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# Posterior pituitary abnormalities caused by pituitary tumors

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**Abstract**

The posterior pituitary gland tightly controls water balance. Before surgery, pituitary adenomas-no matter how large-almost never cause diabetes insipidus, and very rarely cause the syndrome of inappropriate ADH secretion (SIADH). Conversely, disorders of water metabolism are a relatively common complication of surgery for pituitary adenomas. These abnormalities are most often transient, but require careful monitoring and expert management in order to avoid potentially dangerous abrupt variations of blood sodium levels. In this article we will review such abnormalities, and the best way to diagnose and treat them promptly.

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## Introduction

According to the CBTRUS (Central Brain Tumor Registry of the United States) pituitary adenomas are the second most common group of intracranial neoplasms after meningiomas, accounting for approximately 16% of all primary brain tumors [1]. While the majority of pituitary adenomas are non-secreting, the most frequent hormone secreting tumors secrete prolactin. Prolactinomas are usually treated medically, but other secretory pituitary adenomas (GH, ACTH, and TSH) and non-functioning adenomas that cause mass effect on the surrounding structures (mainly the optic chiasm) are treated surgically, with a majority of cases performed via the transsphenoidal approach.

The posterior pituitary ("neurohypophysis") is mostly a collection of axonal projections from the supraoptic and paraventricular hypothalamus nuclei that terminate behind the anterior pituitary. This area serves as site for the secretion of the neurohypophysial hormones oxytocin and antidiuretic hormone (ADH-also called vasopressin) directly into the bloodstream.

Oxytocin is thought to play a role in social bonding, but its best known role relates to delivery and childbirth. It is released into the bloodstream in response to stretching of the cervix during labor, and it causes uterine contraction, helping its progression. Another stimulus to its secretion is the stimulation of the nipples from breastfeeding, and this allows for contraction of myoepithelial cells in the breast and release of milk [2].

ADH is a major regulator of water balance. Under normal circumstances, plasma osmolality is tightly controlled by the secretion of ADH and by the thirst center. ADH is synthesized as a prohormone in the hypothalamus. After synthesis, the prohormone is packaged into neurosecretory granules that are transported down the pituitary stalk to be stored in the posterior pituitary. During this transport, the prohormone is enzymatically cleaved into ADH, neurophysin, and a C-terminal glycopeptide (copeptin). Once released, ADH binds to V2 receptors in the renal collecting duct, thereby stimulating the insertion of Aquaporin water channels into the apical membrane of collecting duct epithelial cells that allow passive reabsorption of water from the renal medulla following osmotic gradients [2]. An additional effect of ADH is vasoconstriction (mediated by V1 receptors). Two main stimuli for ADH release exist: one comes from the baroreceptors in the carotid arteries and aortic arch that are able to sense decreases in blood pressure and circulating blood volume. A more powerful stimulus for is an increase in plasma osmolality, with the osmotic threshold for ADH secretion usually set at about 285 milliosmole (mOsm)/kg $H_2O$. Osmoreceptors in the hypothalamus can sense small changes in plasma osmolality, with changes of 1% or less triggering release of ADH and resulting in increase in urine osmolality. It is estimated that each 1 mOsm/kg $H_2O$ increase in plasma osmolality causes an increase in plasma ADH level between 0.4 pg/mL and 0.8 pg/mL [3]. Other factors can also trigger ADH release, including nausea, pain medications, angiotensin II, histamine, dopamine, bradykinin, and acetylcholine.

Because the synthesis of ADH occurs in the hypothalamus, and the posterior pituitary acts only as a reservoir

for the hormone, no matter how large, pituitary adenomas almost never cause diabetes insipidus (DI) [4]. Accordingly, the presence of DI in a patient with a sellar mass who has not already undergone surgery should prompt the suspicion of a non-adenomatous mass, such as craniopharyngioma, granulomatous or inflammatory disease, or metastatic process (although most often seen in patients with metastases in other locations, the pituitary may be the only site of metastasis). Similarly, although the syndrome of inappropriate ADH secretion (SIADH) may be caused by a pituitary macroadenoma, the presence of hyponatremia in a patient with a macroadenoma is more likely secondary to central adrenal insufficiency and central hypothyroidism than to SIADH.

Conversely, alteration of the function of the posterior pituitary occur rather frequently in the days after pituitary surgery, and this is the aspect on which this article will focus.

## Disorders of water metabolism after pituitary surgery

Disruptions in water regulation can be linked to anatomic or functional injury to the hypothalamus, pituitary stalk, or posterior pituitary gland during surgery. These disorders can occur due to decrease in ADH release leading to DI, or excess ADH release leading to water retention and SIADH. Very rarely, the "cerebral salt-wasting syndrome" (CWS), an ADH-independent condition, can occur after pituitary surgery.

### Diabetes insipidus

Transient DI is relatively common immediately after pituitary surgery. DI is defined as the concomitant presence of hypotonic polyuria (urine output >3 L/24 h and urine osmolality <300 mOsm/kg $H_2O$) in the presence of normal or high serum sodium [5]. While the diagnosis is most of the times obvious, it has to be remembered that other causes of polyuria can be present in the immediate days after pituitary surgery. One is the frequent intraoperative administration of large amounts of fluids. Hyperglycemia can be present, sometimes worsened by glucocorticoid therapy, and —in acromegaly patients— the rapid drop of GH levels can cause significant diuresis. Serum hyper osmolality and hypernatremia can be absent if the patient is conscious and has free and unlimited access to water [3]. While ADH measurement is technically challenging, a promising test (not yet routinely available) to diagnose DI is the measurement of serum copeptin, the N-terminus of ADH prohormone [6].

Postoperative DI can be transient or permanent, and partial or complete, depending on the kind and extent of the damage to hypothalamic magnocellular neurons. DI occurs in 10—30% of patients undergoing pituitary surgery, but it persists long-term only in 2—7% [7—9] (depending from the skill of the surgeon), with approximately 50% of patients remitting in one week and about 80% in three months [10]. Persistence of DI implies that at least 85—90% of hypothalamic magnocellular neurons have been damaged by surgery. The risk of permanent DI is higher in young patients, in males, those with large intrasellar masses and postoperative CSF leak [3,11], and after repeated pituitary surgery [9]. The prevalence of DI is much higher (about 60%) after craniopharyngioma surgery, particularly in pediatric patients [12].

When DI occurs, polyuria typically starts within the 12—24 h after surgery. Acute disorders of water metabolism can manifest in a typically triphasic pattern (typical, but only occurring in a minority of patients): after an initial DI phase, a subsequent SIADH phase (with hyponatremia) develops, and a final DI phase that is usually chronic returns [13]. However, the SIADH phase may be isolated and neither preceded nor followed by DI. While DI is an important problem, in the vast majority of patients (who are awake and have an intact thirst mechanism) it is not dangerous. Adipsic DI (DI associated with lack of thirst perception) is exceedingly rare after pituitary surgery [14]. Conversely, post-surgical SIADH may be dangerous, due to the rapid development of hyponatremia that may cause brain edema, resulting in neurological symptoms that can progress even to seizures and death due to herniation.

To screen for potential development of postoperative DI, in the immediate postoperative period we routinely measure urine output and fluid intake, urine specific gravity daily, and serum sodium every 12 h. For treatment of DI during the immediate postoperative period, we use "as needed" subcutaneous vasopressin injections (typically 5 units), with frequent re-assessment of response (in terms of urine output) to avoid the risk of administering an antidiuretic hormone when transient DI has resolved. We favour the use of native vasopressin at this stage because of its short duration of action. We use as little vasopressin as possible to avoid inducing hyponatremia in light of animal data suggesting that hyponatremia may exacerbate injury-induced degeneration of ADH-secreting hypothalamic neurons [15].

If a patient has persistent DI at the time of discharge from the hospital (typically 2—4 days after surgery) patients are treated with a longer-acting ADH analogue (1-desamino-8-D-arginine vasopressin-DDAVP, also called desmopressin). DDAVP is available as intranasal, oral, and (in some countries) sublingual melts forms. The intranasal form is generally avoided after trans-nasal surgery. While intranasal absorption of DDAVP is about 6%, oral and sublingual absorption rates are less than 1%. A dose equivalence chart of different desmopressin formulations is presented in Table 1 [16].