

Diabetes insipidus as a complication after pituitary surgery

Jennifer A Loh and Joseph G Verbalis*

SUMMARY

Background A 28-year-old woman presented with new-onset vertigo and diplopia that had started 2 weeks previously. An MRI scan of the brain revealed an 11 × 9 × 9 mm sellar mass that extended into the suprasellar region. Evaluation of pituitary function showed mild central hypothyroidism and secondary adrenal insufficiency. The patient underwent trans-sphenoidal resection of the mass without any significant intraoperative complications. On postoperative day 1 she abruptly developed polyuria, hypernatremia and urine hypo-osmolality.

Investigations Measurements of plasma and urine osmolality, urine specific gravity, and serum sodium levels.

Diagnosis Postoperative diabetes insipidus with a triphasic pattern.

Management The patient's diabetes insipidus was initially treated with intravenous desmopressin, and her fluid status, serum sodium levels, and serum and urine osmolality were carefully monitored. During the second, antidiuretic phase, desmopressin was discontinued and the patient's fluid intake was restricted. After recurrence of diabetes insipidus during the third phase, the patient was treated with intranasal desmopressin and was discharged. She remains on desmopressin therapy for chronic diabetes insipidus.

KEYWORDS desmopressin, diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion, trans-sphenoidal surgery, triphasic response

CME

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THE CASE

A 28-year-old woman with a history of irritable bowel syndrome and idiopathic gastroparesis that required percutaneous endoscopic gastrostomy tube feeds presented with a 1-month history of abdominal pain, nausea, and vomiting. She also complained of new-onset vertigo and diplopia that had started 2 weeks previously. An MRI scan of the patient's brain showed an 11 × 9 × 9 mm sellar mass that extended into the suprasellar region (Figure 1A). Her pituitary function was evaluated and showed an abnormal response to an adrenocorticotrophic hormone stimulation test, with a baseline morning cortisol level of 52.42 nmol/l (normal range 184.85–618.02 nmol/l), a 30 min cortisol level of 281.42 nmol/l and a 60 min cortisol level of 372.47 nmol/l.

The patient's prolactin level was mildly elevated at 1,434.77 pmol/l (normal range 121.74–1,269.56 pmol/l). Thyroid function tests revealed mild central hypothyroidism, with free T₄ levels of 9.78 pmol/l (normal range 7.46–21.11 pmol/l) and TSH levels of 0.129 mIU/l (normal range 0.34–5.6 mIU/l). A formal visual field test showed no deficits. She was placed on hydrocortisone replacement therapy at a dose of 15 mg in the morning and 5 mg in the afternoon, with levothyroxine 75 µg daily.

The patient underwent trans-sphenoidal resection of her pituitary tumor 3 weeks later without significant intraoperative complications. A postoperative MRI scan showed successful resection of the tumor with a postsurgical cavity in the sella turcica; there was no discernable posterior pituitary bright spot (Figure 1B). The patient's serum sodium concentration on admission was 142 mmol/l (normal range 135–148 mmol/l), and she had a normal creatinine level of 79.56 µmol/l (Figure 2 summarizes the patient's serum sodium concentration, fluid intake and fluid output during her hospital stay).

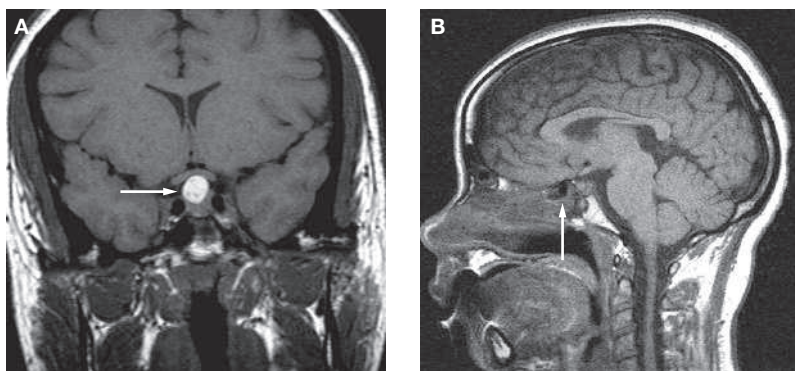


Figure 1 Preoperative and postoperative MRI scans of the patient's pituitary gland. (A) Preoperative MRI scan, coronal view, postcontrast: an 11 × 9 × 9 mm enhancing suprasellar mass is present in the area of the infundibulum (arrow), with mild compression of the superior pituitary and the optic chiasm. (B) Postoperative MRI scan, sagittal view, precontrast: a cyst-like cavity is seen in the sella turcica (arrow) after resection of the suprasellar mass. There is no definitive posterior pituitary bright spot, either within the sella or above it at the base of the hypothalamus.

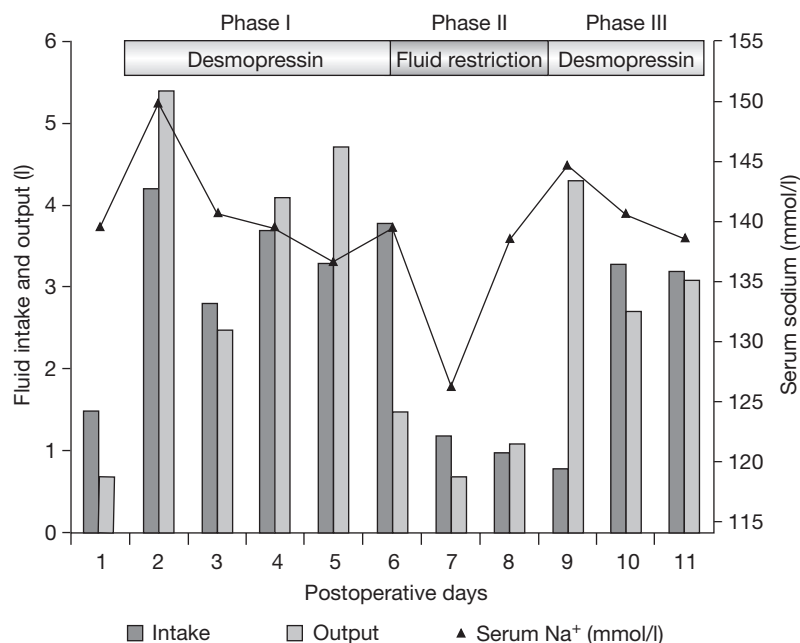


Figure 2 Postoperative pattern of triphasic diabetes insipidus. The fluid intake, urine output and serum sodium level of the patient were recorded on each postoperative day. Postoperative diabetes insipidus began on day 2 and lasted until day 6, when decreased urine output and a fall in serum sodium level signaled the start of the second phase of inappropriate antidiuresis. By day 9, the increased urine output returned, which marked the beginning of the third phase of diabetes insipidus. In this case, diabetes insipidus then became permanent.

On postoperative day 1 the patient's urine output ranged between 30 ml/h and 80 ml/h and her serum sodium level was 138 mmol/l. Late on

postoperative day 1, she began to complain of increased thirst, and her urine output increased briskly to 200–700 ml/h. At that time, her serum sodium level was elevated (150 mmol/l), her plasma osmolality increased to 300 mOsm/kg H₂O, and her urine was dilute (specific gravity 1.003). A diagnosis of diabetes insipidus was made, and the patient was given 1 µg of desmopressin (1-desamino-8-D-arginine vasopressin) intravenously, which resulted in an appropriate decrease of urine output to 25 ml/h, and concentration of urine to a specific gravity of 1.018. By postoperative day 2, her serum sodium level had normalized (140 mmol/l).

Over the next 6 days, the patient's fluid intake and urine output were carefully monitored, and her serum sodium level and urine specific gravity were measured every 4 h. The patient was given 1 µg of intravenous desmopressin whenever her urine output was greater than 250 ml/h for two consecutive hours; she required approximately 1 µg of intravenous desmopressin every 12 h. Her serum sodium level ranged between 137 mmol/l and 142 mmol/l. Her thirst mechanism was intact, and she was able to compensate for the increased fluid loss through oral intake.

On postoperative day 6, the patient's serum sodium level decreased abruptly (from 143 mmol/l to 127 mmol/l) over 20 h. Her urine output decreased to 30 ml/h and her urine specific gravity increased to 1.019. The patient, however, manifested no symptoms of acute hyponatremia. Desmopressin therapy was discontinued and the patient's fluid intake was restricted to 1 l per day. Her serum sodium level increased by 10 mmol/l over the next 24 h, and then by an additional 6 mmol/l over the next 20 h. Her urine specific gravity gradually decreased to 1.007 during this period.

On postoperative day 9, the patient again began to complain of extreme thirst and her urine output abruptly increased to 300 ml/h. Her serum sodium level was 145 mmol/l with a plasma osmolality of 298 mOsm/kg H₂O, and she had a urine specific gravity of 1.004. She was again treated with 1 µg of intravenous desmopressin, which resulted in an appropriate decrease in diuresis, and continued to require 1 µg of intravenous desmopressin every 12 h. The patient was eventually discharged on 10 µg of intranasal desmopressin every 12 h. During a follow-up visit to the endocrine clinic 1 week after discharge, she described normal urine volumes, and had a serum sodium level that was within the normal range.

DISCUSSION OF DIAGNOSIS

Hypotonic polyuria is a very common complication of trans-sphenoidal surgery that occurs in 18–31% of patients postoperatively.^{1,2} Factors found to increase the risk of postoperative diabetes insipidus include young age, male sex, large intrasellar mass, cerebrospinal fluid leak and resection of certain types of lesions, including craniopharyngiomas, Rathke-cleft cysts and adrenocorticotrophic-hormone-secreting pituitary adenomas.^{1,2} The course of postoperative diabetes insipidus can be transient, permanent, or triphasic, as described in classic studies of pituitary stalk transection.³ In most cases, the disease is transient; only 2–10% of patients manifest prolonged polyuria.^{1,2} This symptom is mostly a result of the fact that diabetes insipidus is permanent only if more than 80–90% of the arginine vasopressin (AVP)-secreting neurons in the supraoptic and paraventricular hypothalamic nuclei degenerate bilaterally.⁴

Transient diabetes insipidus almost always begins within 24–48 h of surgery, and usually abates within several days. Both transient diabetes insipidus and the first phase of the triphasic pattern are thought to be caused by temporary dysfunction of AVP-producing neurons, secondary to the connections between the magnocellular cell bodies and the nerve terminals in the posterior pituitary, or to axonal shock from perturbations in the vascular supply to the pituitary stalk and posterior pituitary (Figure 3). Transient diabetes insipidus usually resolves when AVP-secreting neurons recover their normal function.

The triphasic pattern is relatively uncommon, and occurs in 3.4% of patients who undergo trans-sphenoidal surgery; only the first two phases occur in 1.1% of patients.¹ The first phase of diabetes insipidus typically lasts for 5–7 days, and is followed by a second, antidiuretic phase of the syndrome of inappropriate antidiuresis (SIADH), as in the case reported here. This second phase is caused by an uncontrolled release of AVP from either degenerating posterior pituitary tissue, or from the remaining magnocellular neurons whose axons have been severed (Figure 3).^{3,4} In this phase, the urine becomes concentrated and urine output markedly decreases. Continued administration of excess water during this period can quickly lead to hyponatremia and hypo-osmolality, as occurred in this patient on postoperative day 6. The duration of the second phase is variable

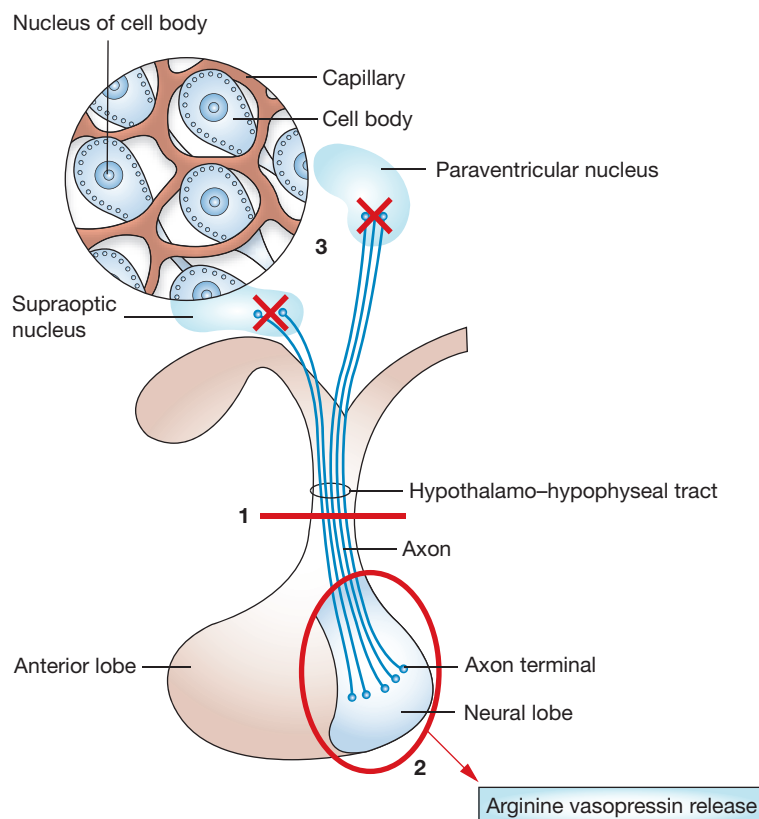


Figure 3 Mechanisms that underlie the pathophysiology of the triphasic pattern of postoperative diabetes insipidus. (1) The first phase of diabetes insipidus is initiated by a partial or complete pituitary stalk section, which severs the connections between the cell bodies of AVP-secreting neurons in the hypothalamus and their nerve terminals in the posterior pituitary gland, which prevents AVP secretion. (2) This first phase is followed, after several days, by the second phase of inappropriate antidiuresis, which is caused by an uncontrolled release of AVP into the bloodstream from the degenerating nerve terminals in the posterior pituitary. (3) After all of the AVP stored in the posterior pituitary gland has been released, a third phase of diabetes insipidus develops if >80–90% of the AVP-secreting neuronal cell bodies in the hypothalamus have degenerated (the figure shows normal AVP-secreting neurons). Abbreviation: AVP, arginine vasopressin.

(2–14 days).⁴ In the case reported here, the duration of antidiuresis was relatively short (<48 h), probably because the large intrasellar mass had already destroyed much of the posterior pituitary, which resulted in a reduced residual store of AVP.

Some patients with limited damage to the neurohypophysis manifest an ‘isolated’ second phase,⁵ in which only SIADH occurs, without any previous or subsequent diabetes insipidus. An isolated second phase is reported to cause hyponatremia in 8–21% of patients after pituitary surgery.^{1,6} After AVP stores are depleted, the third phase of chronic diabetes insipidus

often, but not always,¹ ensues. In this phase, the number of neurons that remain capable of synthesizing AVP is insufficient, which results in permanent diabetes insipidus (Figure 3). Previous studies showed that the major determinant of whether diabetes insipidus following transection of the pituitary stalk is permanent is related to the level of the lesion: the closer the lesion is to the AVP-secreting neurons' cell bodies in the hypothalamus, the more likely it is that the cell bodies will degenerate.⁷

The diagnosis of diabetes insipidus should be considered when a patient excretes large volumes of dilute urine after neurosurgery, typically >2.5 ml/kg body weight per hour. When this symptom is noted, several other potential clinical scenarios should be considered as well. First, patients who undergo surgery in the suprasellar region often receive stress doses of glucocorticoids to prevent secondary adrenal insufficiency. If steroid-induced insulin resistance causes hyperglycemia, the resulting osmotic diuresis from glucosuria can be confused with diabetes insipidus. Urine and blood glucose should, therefore, be measured and any elevated glucose levels should be controlled to eliminate osmotic diuresis as a cause of the polyuria.

Second, excess fluid is sometimes administered intravenously during the perioperative period, which is normally excreted postoperatively. If the large postoperative diuresis is matched with continued intravenous fluid infusions, then a diagnosis of diabetes insipidus based on the resulting hypotonic polyuria is incorrect. If the serum sodium level is not elevated concomitantly with the presence of polyuria, the rate of parenteral administration of fluid should be slowed, and the serum sodium level and urine output should be carefully monitored. The diagnosis of diabetes insipidus can be confirmed by continued hypotonic polyuria in the presence of hypernatremia and/or hyperosmolality.⁸

The diagnosis of postoperative diabetes insipidus is based on both clinical and biochemical data. Patients characteristically complain of the abrupt onset of polyuria and polydipsia, usually in the first 24–48 h after neurosurgery,⁴ and often describe a craving for ice-cold water, which quenches osmotically stimulated thirst well. Urine studies should reveal hypotonic urine, with specific gravity <1.005 or urine osmolality <200 mOsm/kg H₂O. Urine output is typically voluminous (4–18 l daily). Serum hyperosmolality and hypernatremia also strongly

support the diagnosis of diabetes insipidus. Most patients, however, have intact thirst mechanisms, so as long as they have free access to oral fluids, they do not present with either hyperosmolality or hypernatremia.⁹ Consequently, it is often necessary to limit the patient's fluid intake until either hyperosmolality and/or hypernatremia develops, in order to confirm a diagnosis of diabetes insipidus.

MRI can also facilitate the diagnosis of diabetes insipidus. The presence of vasopressin and oxytocin is normally shown as a bright spot in the posterior pituitary on T₁-weighted (contrast-enhanced) images. The lack of a posterior pituitary bright spot can help to confirm a diagnosis of postoperative diabetes insipidus.¹⁰ The bright spot, however, might still be seen at the early phases of this disease,¹¹ so its presence does not exclude a diagnosis of diabetes insipidus. Given that this patient had clinical symptoms of diabetes insipidus, in her case the absence of a pituitary bright spot on the MRI scan (Figure 2B) supported the diagnosis.

TREATMENT AND MANAGEMENT

Treatment of postoperative diabetes insipidus should be individualized (Box 1). Optimally, patients should be monitored for the development of polyuria or hypo-osmolality. Fluid intake and output should be carefully recorded, and patients questioned about their thirst. Once the diagnosis of diabetes insipidus has been confirmed as described above, antidiuretic hormone therapy should be initiated.

Desmopressin is the drug of choice for acute and chronic treatment of central diabetes insipidus.¹² Treatment results in a prompt reduction of urine output and antidiuresis, which generally lasts 6–12 h. It is important to monitor urine osmolality and volume and serum sodium level at frequent intervals to ensure that hypernatremia improves, and to determine when repeat dosing should occur. In order to avoid fluid retention and hyponatremia, each dose of desmopressin should be given after the recurrence of polyuria, but before the patient actually becomes hyperosmolar. In general, urine excretion of 200–250 ml/h with osmolality <200 mOsm/kg H₂O or specific gravity <1.005 affirms the need for repeated treatment with desmopressin.¹³

Administration of desmopressin on an as-needed basis rather than according to a fixed schedule also has the benefit of allowing the detection of decreased polyuria as the

dose wears off, which indicates the return of endogenous AVP secretion. Even this strategy, however, will not always prevent the occurrence of hyponatremia during the second phase of SIADH, as occurred in this case. Whether as part of a triphasic pattern or caused by desmopressin treatment, it is important to note that in a large series of patients who underwent transphenoidal surgery, 8.4% developed hyponatremia at some time up to the 10th day postoperatively, and 2.1% experienced symptomatic hyponatremia.¹ Consequently, serum sodium levels should be measured at regular intervals in all postoperative patients. If hyponatremia does develop during desmopressin therapy, it is especially important to suspend this treatment until the serum sodium level returns to the normal range as a result of the ensuing aquaresis. Failure to allow this correction, either by continuing desmopressin therapy or by replacing the free water excreted, can lead to cerebral edema with catastrophic consequences.¹⁴

Some clinical centers use a continuous intravenous infusion of dilute AVP to treat postoperative diabetic insipidus, particularly in children. Infusions of 0.25–2.70 mU/kg/h have been described to decrease polyuria within 4 h.¹⁵ AVP has a short half-life (10–20 min), and consequently its pharmacologic action can be rapidly terminated if necessary. We prefer to use intermittent doses of desmopressin, because AVP can increase blood pressure when administered intravenously, the use of a continuous infusion requires close monitoring, and it can be difficult to titrate a continuous infusion to achieve the desired urine output. Adverse effects of desmopressin are relatively uncommon, mild, and generally dose-related. Importantly, desmopressin has virtually no pressor effect, since it selectively binds to AVP V₂ receptors but not to AVP V_{1a} receptors on vascular smooth muscle cells. Desmopressin is, therefore, safe to use in patients with coronary or hypertensive cardiovascular disease.¹¹

Fluid replacement is also important in the management of patients with postoperative diabetes insipidus. If the patient is awake and has an intact thirst mechanism, the patient's own thirst is the best guide to their water replacement needs. Increases in plasma osmolality of 2–3% trigger the sensation of thirst, which prevents significant hyperosmolality.¹⁶ If the patient is unable to respond to thirst, fluid balance can be maintained by intravenous fluids. The water deficit can be estimated by a mathematical

Box 1 Treatment of postoperative diabetes insipidus.

Expectant monitoring

- Accurate recording of fluid intake and output
- Measurement of urine osmolality or specific gravity every 4–6 h, until resolution or stabilization
- Measurement of serum sodium levels every 4–6 h, until resolution or stabilization

Antidiuretic hormone therapy

- Desmopressin given intravenously or subcutaneously at an initial dose of 1–2 µg
- Repeat the desmopressin dose when urine output is 200–250 ml/h for ≥2 h with urine specific gravity <1.005 or urine osmolality <200 mOsm/kg H₂O

Maintenance of fluid balance

- Allow the patient to drink according to their thirst
- Supplement with hypotonic intravenous fluids—5% dextrose in water, followed by 5% dextrose in 0.45% (half-normal) saline—if the patient is unable to maintain normal plasma osmolality and serum sodium levels through drinking

Monitor for resolution of transient diabetes insipidus or triphasic response

- Positive daily fluid balance >2 l suggests inappropriate antidiuresis
- Antidiuretic hormone therapy should be suspended and fluids restricted to maintain serum sodium levels within the normal range

Manage anterior pituitary insufficiency

- Administer stress-dose corticosteroids (hydrocortisone 100 mg intravenously every 8 h, tapered to an oral dose of 15–30 mg daily) until anterior pituitary function can be fully evaluated

formula: $0.6 \times ([\text{serum sodium concentration} \div 140] - 1)$. This formula is, at best, an estimate of the patient's fluid requirements; their serum electrolytes should, therefore, be measured frequently (e.g. every 6–8 h) to ensure that fluid replacement is sufficient. Although the development of hyperosmolality is due to water loss in most cases, a careful analysis of tonicity balance reveals that infused sodium can contribute to a hyperosmolar state in the immediate postoperative period.¹⁴ Consequently, all sodium-containing intravenous fluids should be avoided, unless there is clear evidence of hypovolemia.

Competing interests

The authors declared they have no competing interests.

Patients with chronic diabetes insipidus can be treated with intranasal desmopressin. The reliability of intranasal desmopressin can be diminished in patients with mucosal atrophy, congestion, scarring or nasal discharge, so it is advisable to wait several days postoperatively before starting intranasal desmopressin, especially in patients with nasal packing. Treatment should be designed to minimize polyuria and polydipsia, while avoiding hyponatremia due to overtreatment. It is often useful to permit intermittent polyuric episodes every 1–2 weeks by delaying a dose of desmopressin, to verify the continued presence of diabetes insipidus and to allow excretion of any retained excess water. Oral desmopressin has also been shown to be an effective treatment for central diabetes insipidus, and can be useful in patients with mucosal atrophy or scarring. Most patients require an oral desmopressin dose that is 20 times higher than the intranasal dose, because >99% of the oral desmopressin is destroyed by gastrointestinal peptidases. Most patients with central diabetes insipidus require 200–400 µg of oral desmopressin 2–4 times per day to control polyuria.⁸

Finally, as a practical consideration, any patient with postoperative diabetes insipidus should be presumed to have anterior pituitary insufficiency as well, and should receive corticosteroid replacement therapy. In the immediate postoperative setting, hydrocortisone (50–100 mg intravenously every 8 h) is generally used, which is then rapidly tapered to a maintenance dose (15–25 mg daily) until anterior pituitary function can be definitively evaluated.

CONCLUSIONS

Postoperative diabetes insipidus is a common, although usually transient, complication of neurosurgical procedures performed in the sellar and suprasellar region. Patients should be monitored closely after surgery for the abrupt onset of hypotonic urine excretion and/or hyperosmolality. Once a diagnosis of diabetes insipidus is confirmed—using established criteria—patients are best treated with single doses of parenteral desmopressin in order to decrease polyuria and minimize the occurrence of

hyponatremia due to overtreatment. Recognition of the characteristics associated with the triphasic pattern of postoperative diabetes insipidus is important, so that if this condition occurs, the second phase of inappropriate antidiuresis is appropriately managed to prevent severe or symptomatic hyponatremia. Hyponatremia can also occur owing to overtreatment with desmopressin and hypotonic fluids. Patients in whom more than 80–90% of functional AVP-secreting neurons in the hypothalamus are destroyed develop chronic diabetes insipidus; these patients are best managed with long-term administration of intranasal or oral desmopressin.

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