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Review

Diabetes insipidus following resection of pituitary tumors

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ABSTRACT

Diabetes insipidus (DI) is a common complication following pituitary surgery and can be transient or permanent. Neurogenic DI occurs following injury to the magnocellular neurons in the hypothalamus that produce and transport arginine vasopressin (AVP) and form the hypothalamo–hypophyseal tract. DI is defined by a constellation of signs and symptoms resulting in dilute high-volume urine output and increasing serum osmolality. The body's inability to concentrate urine leaves the patient dehydrated and leads to metabolic abnormalities that can be life threatening if not recognized and treated in a timely manner with an exogenous AVP analog. The reported incidence of postsurgical central DI varies from 1 to 67%. This wide range likely reflects inconsistencies in the working definition of DI across the literature. Factors affecting the rate of DI include pituitary tumor size, adherence to surrounding structures, surgical approach, and histopathology of pituitary lesion. The likelihood of postoperative DI can be reduced by careful preservation of the neurovascular structures of the hypothalamus, infundibulum, and neurohypophysis. Vigilance and meticulous surgical technique are essential to minimize injury to these critical regions that can lead to postsurgical DI.

Contents

1. Introduction

Diabetes insipidus (DI) is a common complication following pituitary surgery. This condition can be transient or permanent and the signs and symptoms of this disorder can be mimicked by the normal postoperative course. Understanding the hypothalamic–pituitary axis is important in distinguishing a normal postsurgical course from abnormal responses that need to be medically treated. In this review, we discuss the anatomic and physiologic aspects of arginine vasopressin (AVP); the incidence, diagnosis and management of DI following pituitary surgery; the treatment options available; as well as possible perioperative preventative measures.

2. Antidiuretic hormone: anatomic and physiologic aspects

AVP is a nanopeptide that is synthesized primarily in the magnocellular neurons of the supraoptic and paraventricular hypothalamic nuclei. Axonal projections from these neurons form the hypothalamo–hypophyseal tract, which terminates in the

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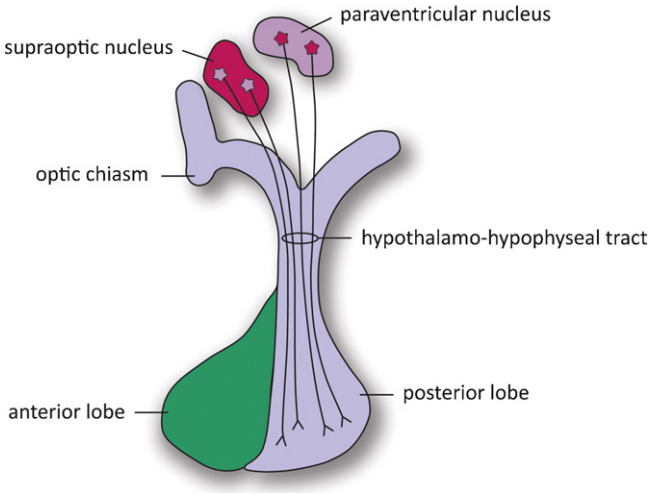

Fig. 1. Arginine vasopressin is produced by magnocellular neurons in the supraoptic and paraventricular nuclei of the hypothalamus and is transported to the neurohypophysis via the hypothalamo–hypophyseal tract. Injury to these structures can lead to transient or permanent DI.

posterior lobe of the pituitary gland (Fig. 1). AVP, also known as antidiuretic hormone (ADH), is transported in an anterograde fashion within neurosecretory granules to the neurohypophysis, where it is released into the bloodstream in its physiologically mature form as needed [1].

AVP exerts its action by binding to the vasopressin V2 receptor (V2R) on the basal aspect of the renal collecting tubular cell [2]. This leads to an intracellular signaling cascade that concludes with activation of a cyclic adenosine monophosphate kinase pathway which increases production and insertion of aquaporin-2 channels into the cell membrane [2,3]. This, in turn, leads to increased passive resorption of water from the lumen of the nephron into the cells of the collecting duct along an osmotic gradient [4]. Aquaporins-3 and -4 allow this water to pass from the cells into the renal interstitium and then into the circulation [2]. AVP also acts to increase interstitial osmolality by facilitating increased urea reabsorption from the medullary lumen [5]. Under normal conditions, water balance is controlled via renal excretion and absorption of water so as to maintain plasma osmolality in the range of 280–295 mOsm/kg. Three related factors regulate water balance in healthy humans: renal function, AVP levels, and thirst. Plasma osmolality regulates the release of AVP whereby an increase in the osmolality leads to increased AVP release and a decrease in plasma osmolality inhibits further AVP release [6,7]. Other factors that regulate release of AVP include changes in blood pressure, nausea, hypoglycemia, morphine, ethanol, and nicotine, but these are, in general, less sensitive than serum osmolality [6]. In instances where there is excessive fluid loss and AVP has maximized its urinary concentrating abilities, water balance is regulated by increased fluid intake as a result of activation of the thirst mechanism. The sensation of thirst is dependent on plasma osmolality in a manner similar to AVP [8].

3. Clinical manifestations of diabetes insipidus

Diabetes insipidus is a condition in which the kidneys are unable to or not signaled to conserve water via AVP stimulation. The primary clinical manifestations of DI are polyuria and polydipsia, especially for cold water [9]. DI can be suspected when these clinical signs and symptoms are present. However, the diagnosis is confirmed with the aid of adjuvant laboratory tests. DI that goes unrecognized can progress to hypernatremia and hyperosmolarity, progressive signs and symptoms including dehydration, lethargy, irritability, and, in the case of severe hypernatremia, seizures [10].

There are two subtypes of DI: nephrogenic and neurogenic. Nephrogenic DI occurs when there is an inadequate response to AVP in the renal tubules, leading to an inability to concentrate urine; this can be caused by certain drugs, hypercalcemia, and primary kidney diseases [11]. Neurogenic (or central) DI occurs when there is inadequate secretion of AVP from the hypothalamus. This can be hereditary, idiopathic, or due to injury to the hypothalamus, neurohypophysis, or hypothalamo–hypophyseal tract. Causes of injury include neoplastic or autoimmune disease, trauma, radiation, infection, ischemia, hemorrhage, and surgical manipulation [9]. In addition, various inherited and congenital diseases have been associated with neurohypophyseal DI including familial central DI, Wolfram syndrome, congenital hypopituitarism, and septo-optic dysplasia [12]. In this review, we focus on neurogenic DI related particularly to pituitary tumors and following transsphenoidal surgery.

4. Diabetes insipidus after pituitary surgery

Polyuria is common after transsphenoidal surgery; however it is not always due to DI. In fact, the most common cause of polyuria in the postoperative setting is diuresis of intravenous fluids administered in the perioperative period. Other causes of postsurgical polyuria include hyperglycemia and diuretic administration. These should be considered and excluded before treatment of DI is initiated. Also, acromegalic patients have been known to have increased urinary output following resection of the pituitary microadenoma due to diuresis of excess fluid in the soft tissues [10,13].

Nevertheless, polyuria remains a hallmark of DI. As such, accurate measurement of urine output is critical. When DI is suspected, additional tests are needed to confirm the diagnosis including measurement of urine specific gravity, urine and serum osmolality, and serum sodium. A diagnosis of DI is contingent upon the presence of polyuria and polydipsia in conjunction with specific laboratory abnormalities. Unfortunately, there are a wide range of measurements that have been used to establish a diagnosis of DI in the literature. For example, various authors have reported different thresholds of elevated urine output that should raise suspicion for DI, such as >2 ml/kg/h [14], >30 ml/kg/day [15], 2.5–18 L/day [10,16–18], and >250–500 ml/h for 2–3 consecutive hours [4,15,19,20]. Urine specific gravity <1.005 is often used as a diagnostic parameter of DI [4,10,15–19]. Urine osmolality <300 mOsm/kg and serum osmolality >300 mOsm/kg are also thought to be diagnostic of DI [14,15,20,21]. In addition, one should be suspicious of DI when serum sodium increases to levels >140–145 mequiv/L [14,15,17,18,20]. A low-to-absent serum AVP level is diagnostic of central DI; though it is rarely used in the clinical diagnosis of the postoperative patient because the time required to obtain results can be a week or longer if the samples must be sent to a central facility. This timeframe is unacceptable for a patient who could become clinically unstable if his or her DI is left untreated. Ultimately, the diagnosis of DI in the postoperative period is made by the clinical picture together with the constellation of abnormal laboratory values.

Postoperative DI can follow one of three courses: transient, permanent, and triphasic. Transient DI begins with an abrupt onset of polyuria within 24–48 h of surgery and gradually resolves over a 3–5 day period [4,14]. Permanent DI can be seen in patients in whom there is damage to the hypothalamus or proximal infundibulum [14]. The third possible course, a triple-phase response (Fig. 2), was first described by Fisher and Ingram [22]. The first phase, which is identical clinically to transient DI, begins within 24 h of surgery and typically lasts for 4–5 days. This occurs as a result

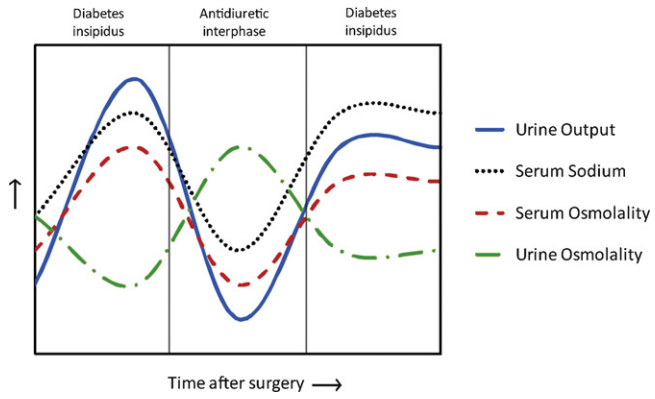

Fig. 2. The triphasic response starts with symptoms of DI caused by "stunning" of the magnocellular neurons and a lack of AVP secretion. This initial phase is followed by a period of increased AVP secretion whereby the injured hypothalamic cells degenerate and release their stored AVP. At the end of this antidiuretic interphase, if the majority of AVP-producing neurons are destroyed, a permanent phase of DI begins.

of absent or decreased release of AVP due to hypothalamic neuronal shock. Following this initial response, an interphase occurs beginning around 1 week postoperatively and lasts for approximately 1 week. As injured magnocellular neurons degenerate, they release their remaining AVP stores leading to water retention and decreased urine output. In some patients, hyponatremia and/or hypoosmolality may develop. The interphase is followed by the final phase whereby permanent DI ensues due to complete degeneration of neurons in the supraoptic and paraventricular hypothalamic nuclei [4,13,14,22]. Overall, the triphasic response is relatively uncommon, occurring in only 1–3% of patients undergoing pituitary surgery [16]. Permanent DI occurs when there is loss of 85% or more of the hypothalamic magnocellular neurons. The closer the surgical injury is to the hypothalamus, the more likely neuronal degeneration and cell death will arise.

After transsphenoidal surgery, patients should be closely monitored in an intensive care unit that has experience in caring for neurosurgical patients. In addition to standard postoperative care, patients must be closely observed for signs and symptoms of DI with strict recording of all inputs and outputs. Serum electrolytes and osmolality must be checked daily. If the patient begins to demonstrate polyuria as outlined earlier, serum and urine osmolality, urine specific gravity, and serum sodium should be obtained serially. Body weight should also be recorded on a daily basis to assess overall fluid balance.

5. Endoscopic versus microsurgical approach

Transient DI is commonly seen after transsphenoidal pituitary surgery. With a transnasal microsurgical approach, the rate of transient DI has been reported between 1.6 and 45.6% (Table 1) [10,16,18–21,23–30]. The incidence of temporary DI following a transnasal endoscopic approach has been reported between 2.5 and 15.2% (Table 2) [17,25,29,31–53]. The rates of permanent DI following both microsurgical (0–8.8%) and endoscopic (0–7.1%) approaches are similar. The incidence of transient and permanent DI following the sublabial transseptal approach is 18–58.1% and 0.7–8.2%, respectively (Table 3) [38,47,48,54–58]. Several studies have demonstrated a lower incidence of postoperative DI in patients who underwent endonasal resections compared to those who had sublabial transseptal resections [48,58,59]. Similar studies have shown that the rate of DI is roughly the same between transnasal microscopic resection and transnasal endoscopic resection [4,19].

However, a recent meta-analysis by Goudakos et al. found that postsurgical DI was less frequent in those who underwent endoscopic surgery compared to those who had microsurgical resection (15% vs. 28%, $p = 0.03$) [60]. In contrast, Deklotz et al. performed a meta-analysis of 21 endoscopic studies ($n = 2335$) and 17 sublabial studies ($n = 2565$) [61]. They noted that while the endoscopic approach provided superior outcomes (higher rates of complete tumor resection and lower rates of CSF leak, septal perforation, and postsurgical epistaxis) compared to the sublabial approach, there was no statistical difference in the incidence of DI between the two surgical techniques [61].

A study by Nemergut et al. [19] retrospectively compared the rates of DI following transnasal microscopic resection of various sellar lesions in 881 patients to look for patient- and surgery-specific risk factors for DI. They found that patients with microadenomas were more likely to have transient DI postoperatively; whereas patients with intraoperative CSF leak had a significantly higher risk of having both transient and persistent DI after transsphenoidal surgery [19]. They also found that patients with craniopharyngiomas and Rathke's cleft cysts had higher rates of both transient and persistent DI when compared with the entire patient population. Interestingly, reoperation did not increase the likelihood of developing postsurgical DI. Among those with pituitary adenomas, patients with Cushing's disease were more likely to have transient postoperative DI than those with other adenoma subtypes, but this difference did not persist beyond the immediate postoperative period [19].

Table 1
Incidence of transient and permanent DI following microscopic transnasal transsphenoidal pituitary surgery.

Author	Number of procedures	Number with transient DI (% ± S.D.)	Numbers with permanent DI (% ± S.D.)
Black et al. [23]	255	4 (1.6%)	1 (0.4%)
Chen et al. [24]	385	72 (18.7%)	0
Cheng et al. [25]	59	3 (5.1%)	1 (1.7%)
Fatemi et al. [26]	435	107 (24.6%)	9 (2.1%)
Freda et al. [27]	125	4 (3.2%)	0
Hensen et al. [16]	1571	539 (34.3%)	4 (0.3%)
Kristof et al. [18]	57	26 (45.6%)	5 (8.8%)
Nemergut et al. [19]	743	123 (16.6%)	5 (0.7%)
Nomikos et al. [28]	660	224 (33.9%)	2 (0.3%)
Olson et al. [21]	92	18 (19.6%)	n.a.
O'Malley et al. [29]	25	2 (8%)	2 (8%)
Rajaratnam et al. [20]	114	28 (24.6%)	4 (3.5%)
Semple and Laws [30]	105	12 (11.4%)	1 (1%)
Sheehan et al. [10]	288	76 (26.4%)	4 (1.4%)
Total	4914	1238 (25.2 ± 13%)	38 (0.8 ± 2.9%)

n.a.: not available; S.D.: standard deviation.

Table 2
Incidence of transient and permanent DI following endoscopic transnasal transsphenoidal pituitary surgery.

Author	Number of procedures	Number with transient DI (% ± S.D.)	Numbers with permanent DI (% ± S.D.)
Berker et al. [31]	624	29 (4.6%)	3 (0.5%)
Campbell et al. [32]	26	2 (7.7%)	0
Cappabianca et al. [33]	146	8 (5.5%)	5 (3.4%)
Charalampaki et al. [34]	150	10 (6.7%)	2 (1.3%)
Cheng et al. [25]	68	2 (2.9%)	0
Dehdashti et al. [35]	200	5 (2.5%)	2 (1%)
Frank et al. [36]	381	n.a.	6 (1.6%)
Gondim et al. [37]	341	15 (4.4%)	4 (1.2%)
Graham et al. [38]	66	10 (15.2%)	0
Heilman et al. [39]	34	n.a.	1 (2.9%)
Hofstetter et al. [40]	71	n.a.	5 (7.1%)
Jane et al. [41]	60	2 (3.3%)	3 (5%)
Jho [17]	128	5 (3.9%)	4 (3.1%)
Kabil et al. [42]	200	n.a.	4 (2%)
Kelley et al. [43]	75	7 (9.3%)	n.a.
Muñoz del Castillo et al. [44]	20	2 (10%)	0
O'Malley et al. [29]	25	1 (4%)	0
Rudnik et al. [45]	88	n.a.	2 (2.3%)
Santos et al. [46]	30	1 (3.3%)	2 (6.7%)
Shah and Har-El [48]	26	2 (7.7%)	1 (3.8%)
Sheehan et al. [47]	26	1 (3.8%)	0
Shen et al. [49]	40	2 (5%)	0
Sigounas et al. [50]	110	15 (13.6%)	3 (2.7%)
Yano et al. [51]	213	10 (4.7%)	2 (0.9%)
Zada et al. [52]	169	5 (3%)	0
Zhou et al. [53]	375	14 (3.7%)	n.a.
Total	3692	148 (5.1 ± 3.5%)	49 (1.5 ± 2.1%)

n.a.: not available; S.D.: standard deviation.

6. Treatment options

Treatment of postoperative DI is typically multifaceted and should be individualized for every patient. The goal of treatment is to maintain and/or restore osmotic equilibrium.

6.1. Free water

If the patient is awake and has an intact thirst mechanism, he or she must be provided adequate access to water. As long as the patient is able to consume a sufficient amount of fluids so as to maintain normal serum sodium and osmolality, further action is generally not required [4,9]. This can often be done in the setting of transient DI; however, pharmacotherapy is usually needed while the patient is asleep and unable to maintain the fluid balance.

6.2. Desmopressin

If the polyuric patient is unable to drink an adequate amount of fluids, or there are disturbances of the serum sodium and/or osmolality, and causes of polyuria other than DI have been excluded, then administration of a synthetic analog of AVP, desmopressin (1-deamino-8-D-arginine vasopressin; trade names: DDAVP, Stimate, Minirin) is recommended. Desmopressin has a prolonged antidiuretic action with minimal vasopressor activity and can be administered orally, intranasally, subcutaneously, or intravenously [6]. Dosing of hormone replacement must be done with great vigilance in order to prevent 'overshooting' that can result in hyponatremia [4]. The daily dosing range for the oral preparation varies from 100 to 800 mcg (divided in two to three doses), while the doses for the intranasal and parenteral routes are 10–40 mcg (in two doses) and 2–4 mcg (in one or two doses), respectively [6]. The timing of the doses is not standard and must be individualized. If intranasal packing is placed during surgery, the intranasal form of desmopressin should be avoided. The plasma half-life of desmopressin is around 3 h but its pharmacologic effects can last up to 10 h [62]. Total daily dosage should be titrated to obtain adequate antidiuresis with strict monitoring of the patient's urinary output. One must be cautious to not overshoot the target in patients who continue to drink large quantities of water after administration of desmopressin.

Sheehan et al. [10] retrospectively studied factors that increased the likelihood of using desmopressin postoperatively. They found that women were significantly more likely to require the AVP analog in both the immediate postoperative period and on a long-term basis. Prior pituitary surgery and presence of hypernatremia or polyuria on the first postoperative day were associated with higher desmopressin use in the immediate postoperative period,

Table 3
Incidence of transient and permanent DI following sublabial transseptal pituitary surgery.

Author	Number of procedures	Number with transient DI (% ± S.D.)	Numbers with permanent DI (% ± S.D.)
Abosch et al. [54]	254	54 (21.3%)	4 (1.6%)
Graham et al. [38]	122	28 (23%)	10 (8.2%)
Marazuela et al. [55]	35	n.a.	2 (5.7%)
Mortini et al. [56]	1140	n.a.	8 (0.7%)
Rollin et al. [57]	117	68 (58.1%)	2 (1.7%)
Shah and Har-El [48]	55	16 (29.1%)	4 (7.3%)
Sheehan et al. [47]	44	n.a.	1 (2.3%)
White et al. [58]	50	9 (18%)	2 (4%)
Total	1817	175 (29.3 ± 16.3%)	33 (1.8 ± 2.8%)

n.a.: not available; S.D.: standard deviation.

but did not correlate with later time points. The authors found no correlation between tumor histology and size with incidence of desmopressin use. In contrast, Nemergut et al. [19] noted a positive correlation with increased desmopressin use in patients with microadenomas, those who had intraoperative CSF leaks, and those with craniopharyngiomas or Cushing's disease. This discrepancy may be due to differences in patient populations and threshold for administering desmopressin.

6.3. Other oral drugs

Other oral medications besides desmopressin have been used to treat patients with partial central DI with mixed results. Carbamazepine (an antiepileptic agent) and chlorpropamide (a sulfonylurea) both increase the sensitivity of renal collecting ducts to circulating AVP [9,63]. Carbamazepine is given in doses of 100–400 mg twice daily and chlorpropamide is given once or twice daily at a dose of 3–5 mg/kg [6,63]. These agents are not often used to treat DI as they are less effective than desmopressin and can have significant side effects [14]. Thiazide diuretics can be effective in DI as well. They work by preventing sodium and chloride from being absorbed in the distal renal tubule, which, in turn, allows more sodium, and therefore water, to be absorbed in the proximal tubules [6,63]. The usual dose of hydrochlorothiazide is 50–100 mg/day.

7. Preventative measures

Rajaratnam et al. [20] studied the effects of perioperative hydrocortisone in patients with normal basal levels of cortisol in a prospective, randomized, single-blinded study. Using a protocol with a lower hydrocortisone dose than their institution's standard protocol, they found a nearly 50% reduction in the incidence of DI. The postulated reason for the greater incidence of DI with patients in the high-dose group is that elevated levels of hydrocortisone suppress AVP release. Moreover, the authors noted an appropriate graded cortisol stress response in patients that were not given any perioperative hydrocortisone, with no significant difference in the rate of postsurgical DI when compared to the low-dose hydrocortisone group. This suggests that these patients have a normally functioning hypothalamic–pituitary–adrenal axis and therefore do not need exogenous perioperative steroid coverage. For patients who required hydrocortisone perioperatively, the low-dose protocol (25 mg intravenously at time of induction of anesthesia and every 6 h thereafter on day 1, every 8 h on day 2, and every 12 h on day 3) appeared to be sufficient and reduced the incidence of postoperative DI.

Prevention of DI following transsphenoidal surgery is centered on the preservation of the hypothalamus, infundibulum, and neurohypophysis. However, these critical structures may be compromised as a result of surgical injury or inherent factors related to the pituitary mass such as location, size, and level of adherence to surrounding neurovascular structures. Barker et al. [64] demonstrated that postoperative DI was significantly less frequent with increased hospital and surgeon caseload, suggesting that greater experience leads to lower complication rates.

8. Conclusions

Diabetes insipidus is a common but usually transient complication following pituitary surgery. In rare instances of massive damage to AVP-producing magnocellular neurons of the hypothalamus, a permanent lack of endogenous vasopressin ensues. While certain factors appear to carry a higher risk for postoperative DI, it is important to monitor all postsurgical patients closely in an intensive care setting and to treat DI when appropriate. Other causes of postoperative polyuria must be ruled out, so as to avoid unnecessary pharmacotherapy. Meticulous surgical technique and careful preservation of the critical neurovascular structures in the hypothalamic–pituitary axis are essential in averting postsurgical DI.

Conflict of interest

The authors declare that they have no conflicts of interest.

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