Management of Diabetes Insipidus following Surgery for Pituitary and Suprasellar Tumours

*Mussa H. Almalki,1,2 Maswood M. Ahmad,1 Imad Brema,1 Mohammed Almehthel,1,3 Khaled M AlDahmani,4,5 Moeber Mahzari,2,6 Salem A Beshyah7,8

ABSTRACT: Central diabetes insipidus (CDI) is a common complication after pituitary surgery. However, it is most frequently transient. It is defined by the excretion of an abnormally large volume of dilute urine with increasing serum osmolality. The reported incidence of CDI after pituitary surgery ranges from 0–90%. Large tumour size, gross total resection and intraoperative cerebrospinal fluid leak usually pose an increased risk of CDI as observed with craniopharyngioma and Rathke’s cleft cysts. CDI can be associated with high morbidity and mortality if not promptly recognised and treated on time. It is also essential to rule out other causes of postoperative polyuria to avoid unnecessary pharmacotherapy and iatrogenic hyponatremia. Once the diagnosis of CDI is established, close monitoring is required to evaluate the response to treatment and to determine whether the CDI is transient or permanent. This review outlines the evaluation and management of patients with CDI following pituitary and suprasellar tumour surgery to help recognise the diagnosis, consider the differential diagnosis, initiate therapeutic interventions and guide monitoring and long-term management.

Keywords: Central Diabetes Insipidus; Polydipsia; Polyuria; Pituitary Adenoma; Preoperative Risk Factor; Pituitary Surgery; Arginine Vasopressin; Desmopressin; Treatment.

Pituitary adenomas are the third most common intracranial neoplasm which accounts for 10–15% of all diagnosed intracranial tumours and are frequently treated with transsphenoidal surgery (TSS), except prolactinomas.1 Neurosurgical operations for pituitary and suprasellar tumours may result in postoperative complications due to the crucial anatomical location of these tumours. The resulting postoperative complications can manifest as anterior or posterior pituitary dysfunction, particularly sodium disturbances, due to the changes in antidiuretic hormone (ADH) secretion, which remains one of the most frequent postoperative reasons for hospital readmission.2 The patterns of water and electrolyte disorders after TSS can be divided into either polyuria or oliguria/hyponatremia, depending on the presence of either low or high levels of ADH, respectively.2 Some disturbances of water and electrolytes may not reach the level of clinically defined central diabetes insipidus (CDI) or syndrome of inappropriate antidiuretic hormone (SIADH). However, they may still require acute or chronic management and are generally divided into six profiles of polyuria or hyponatremia as follows: transient or sustained polyuria, immediate or delayed hyponatremia and biphasic or triphasic diabetes insipidus (DI).2,3 CDI manifests as the excretion of large amounts of dilute urine that often occurs in the acute phase following surgery for pituitary adenomas, subarachnoid haemorrhage or traumatic brain injury. Nonetheless, it occurs rarely in association with large pituitary adenomas before surgical interventions. Its occurrence in this setting should question this diagnosis and point towards other diagnoses such as craniopharyngioma or granulomatous diseases.4

Serum sodium and osmolality levels are generally maintained within a very narrow range (within 1–2%) despite marked variations in water and salt intake and is controlled by two mechanisms, namely arginine vasopressin (AVP) and thirst. The development of CDI after TSS for pituitary adenoma is common, but it is usually transient. Most patients who have free access to fluids and have intact thirst mechanisms can maintain normal serum sodium and normal fluid balance, as well as avoid dehydration and hypernatremia that usually result from the development of a significant water deficit. Hence, it is exceptionally vital to frequently monitor the urine output, serum sodium and daily fluid balance in all neurosurgical patients following TSS. When patients have impaired levels of consciousness due to various factors, such as sedation, or if the thirst mechanism is impaired, for example in the rare subtype of adipsic DI, they can develop significant water deficit and severe hypernatremia.5,6

The measurement of copeptin as a surrogate marker for AVP in the diagnostic workup of the three main causes of polyuria (i.e. CDI, nephrogenic...
DI and primary polydipsia) has revolutionised the management approach of the patients with these suspected conditions, given its stable assays, high diagnostic accuracy and high specificity. Due to a paucity of studies comparing different treatment and monitoring strategies for acute CDI following transsphenoidal pituitary surgery, there is a general lack of clear guidelines based on grades of evidence for acute DI following TSS management. Nonetheless, there have been increasing adverse events, including death, which have been highlighted in recent years for the patients with established CDI, mainly due to a lack of knowledge among health professionals dealing with this condition. Hence, there is a need to update the knowledge highlighting all the pitfalls that can lead to adverse patient outcomes.

The rationale for this review article is to present updated information regarding the frequency, predictors of occurrence, clinical presentation and diagnostic workup, including the role of measurement of copeptin, which fills an important gap that exists regarding the limitation of water deprivation test in differentiating between CDI and primary polydipsia. The therapeutic interventions for CDI will also be reviewed, including those used for treating the rare and serious subtype of adipsic DI, as well as the prognosis of CDI following TSS.

**Epidemiology**

CDI is a significant complication following pituitary surgery which has been reported in the medical literature. Transient diabetes insipidus (TDI) has been reported in 1.6–45.6% of the patients after pituitary surgery with a transnasal microsurgical approach and in 2.5–26% of those who had surgery with the transnasal endoscopic approach. Permanent diabetes insipidus (PDI) is less common and has been reported in 0–10% of patients following the microsurgical approach and in 0–12.5% of patients following the endoscopic approach. The evidence is inconsistent regarding whether endoscopic TSS is associated with a lower incidence of DI in comparison to microscopic TSS, with some studies showing a lower incidence while others do not. One study investigated the DI following transcranial pituitary surgery and found the incidence of TDI and PDI to be 21.1% and 12.2%, respectively. CDI is more common after craniopharyngioma surgery and has been reported in up to 90% of the patients. The onset of polyuria is usually abrupt and occurs within the first 12–24 hours after surgery. However, later presentation (two weeks to three months after surgery) has been reported in patients with Rathke's cleft cyst. The pathophysiology of this is not well understood but it has been suggested to be resulting from the release of cyst contents, causing inflammation to the infundibulum.

**Clinical Presentation**

CDI should be considered when a patient excretes large volumes of diluted urine after surgery, typically ranging in 3.5–16.8 L per day, in the presence of high or normal serum sodium and osmolality. The classic triphasic water dysregulation is rare and occurs in approximately 1.1–3.4% of postoperative patients where transient DI, a polyuric phase occurring due to the abrupt cessation of AVP release as a result of the temporary hypothalamic dysfunction, is followed by the second...
phase that resembles SIADH, which is caused by the sudden release of AVP from the degenerating pituitary. Finally, depletion of AVP stores leads to permanent CDI.30–31 The onset of polyuria is usually abrupt and occurs within the first 12–24 hours after surgery. The initial transient phase of DI happens within 1–3 days after surgery and typically lasts for 5–7 days. The second phase ensues 7–8 days postoperatively and can last 2–14 days if there is no recovery of anti-diuretic hormone (ADH)-secreting neurons. The third phase occurs when DI reappears as a result of depletion of ADH stores.32–35

Patients with DI typically complain of persistent excessive thirst and drink to compensate for the water loss to maintain serum sodium within the normal range. However, patients with limited access to water, impaired consciousness level or impaired thirst sensation may rapidly develop signs of dehydration on physical examination in addition to hypernatremia (serum sodium >145 mmol/L) if free water loss is not replaced.36,37

**DIAGNOSTIC WORKUP**

The diagnosis of CDI postoperatively begins with the risk assessment using pre- and intra-operative predictive factors before the patient is transferred from the operation room. Excessive thirst and polyuria are the clinical features that typically trigger an evaluation for CDI.38 Hence, careful documentation of hourly fluid intake and urine output is essential for the early identification of CDI. It is crucial to note that polyuria may not always be due to DI; as seen in cases of mobilisation of intraoperative fluids and hyperglycaemia, it can also be due to a sharp drop of growth hormone level post acromegaly surgery and the use of certain medications such as furosemide or SGLT2 inhibitors.39 Therefore, documentation of hypotonic polyuria is essential in establishing the diagnosis of DI. Seckel and Dunger criteria to diagnose CDI rely on the presence of hypotonic polyuria (urine osmolality <300 mOsmol/kg and urine output more than 2 mL/kg/h) in addition to increased serum osmolality (>300 mOsmol/kg) after excluding other causes of polyuria, such as glucosuria.40 In adult patients in particular, urine output of more than 250 mL per hour for two consecutive hours when supplemented with the presence of normal or high serum sodium, normal or high serum osmolality with a urine osmolality of less than 300 mOsmol/kg is highly suggestive of DI.41 Urine specific gravity is easily assessed at the bedside and could provide a

---

**Figure 1:** Post-pituitary-surgery evaluation (risk-based assessment).

DI = diabetes insipidus; U = urine; S = serum; DDAVP = desmopressin; LOC = level of consciousness; PRN = as needed.

DI Risk: Low = No risk factors; High = Any DI postoperative or intraoperative risk factors.
Moreover, the frequency of monitoring electrolytes is highly variable among physicians. 43 Therefore, frequent assessment of electrolytes and osmolality in patients with a decreased level of consciousness or impaired thirst sensation is necessary for early detection of CDI.

The difficulty in diagnosing CDI, particularly in the immediate postoperative period, has led to the exploration of other ways to diagnose CDI. 44 Plasma AVP measurement has been explored; however, it could be challenging as its half-life is short (16 minutes) and the AVP is usually unstable in collected plasma samples and is affected by many factors leading to its inaccurate level. 45–47 Moreover, AVP measurement with ELISA is not usually feasible due to the small size of AVP. 48 Furthermore, AVP measurement, usually done by rapid acting insulin and requires a relatively large sample volume, is not available in a timely manner to diagnose DI as it requires a relatively long time and specialised labs to process it. For these reasons, AVP measurement is rarely useful in the diagnosis of postoperative DI.

On the other hand, copeptin is the C-terminal peptide of pro-vasopressin, co-secreted with AVP in an iso-osmolar manner, and reflects AVP level accurately. Unlike AVP, copeptin measurement is less cumbersome as it remains stable in collected plasma samples for days and its measurement is associated with less preanalytical errors. 49–50 It is highly accurate in identifying the aetiology of polyuria in the non-acute setting. 51 However, its utility in the post-pituitary-surgery setting has been evaluated in only a few studies. A multicentre study, 50 out of 205 patients who developed CDI revealed that a copeptin level of <2.5 pmol/L is accurate in establishing the diagnosis of CDI with a specificity of 97% and positive predictive value of 81% when measured within 24 hours of surgery. 52 In contrast, a value of >30 pmol/L almost excluded the diagnosis with a negative predictive value of 1.005 suggesting low urine osmolality. 42

However, despite the availability of these tools, the diagnosis of post-pituitary-surgery CDI could be a challenge due to several factors. First, there is a lack of universal diagnostic criteria for DI and enormous variability in the monitoring of patients following pituitary surgery. Moreover, the current diagnostic criteria may not apply to patients who are able to consume water and self-manage CDI, especially if the DI is partial. Furthermore, thin adults could have DI, but their urine output is <200 mL/h, which may delay the diagnosis. For such patients, using weight-based criteria to define polyuria (urine output of >2 mL/kg/h or >50 mL/kg/day) would be more accurate. Additionally, the frequency of monitoring electrolytes and osmolality could be challenging as its half-life is short (16 minutes) and the AVP is usually unstable in collected plasma samples and is affected by many factors leading to its inaccurate level. 45–47 Moreover, AVP measurement with ELISA is not usually feasible due to the small size of AVP. 48 Furthermore, AVP measurement, usually done by rapid acting insulin and requires a relatively large sample volume, is not available in a timely manner to diagnose DI as it requires a relatively long time and specialised labs to process it. For these reasons, AVP measurement is rarely useful in the diagnosis of postoperative DI.

### Table 1: Biochemical parameters in patients with post-operative diabetes insipidus

| Parameter                  | Description                                                                 |
|----------------------------|-----------------------------------------------------------------------------|
| Fluid balance              | Variable, usually negative (more output than input)                         |
| Urine output               | At least >2 mL/kg/h for two consecutive hours in addition to other parameters |
| Serum osmolality           | Normal, if the patient has free access to water, or high, >300 mOsmol/kg, if the patient has limited access to water |
| Serum sodium               | Normal, if the patient has free access to water, or high, >145 mmol/L, if the patient has limited access to water |
| Urine osmolality           | Persistently <300 mOsmol/L                                                  |
| Urine specific gravity     | Persistently <1.005                                                         |
| Copeptin                   | <2.5 pmol/L                                                                 |

### Table 2: General management strategies for a patient with diabetes insipidus

#### Immediate postoperative period

- Assessment of volume and hydration status; measurement of serum sodium
- Close monitoring of serum sodium and urine output
- Optimisation of fluid replacement
- Consideration of desmopressin therapy in a patient with excessive and inappropriately dilute urine output
- Titration of desmopressin dose to keep 24-hour urine output above the normal range (15–30 mL/kg/day)

#### After hospital discharge

- Limiting fluid intake to the amounts required to satisfy thirst
- Performing electrolyte panel checks in any unwell patient after hospital discharge; close postoperative follow-up
- Monitoring for water intoxication and hyponatremia
- Delaying a dose of desmopressin once or twice per week to allow an aquaresis to occur
- Regular counselling of patient and their family about the principle of the treatment regime

### Table 3: Management of hydipsia/adipsia with central diabetes insipidus

- Set a target (kg) at the weight the patient is known to be euvoletic and normonatremic
- Fix 24-hour urine output at 1.5–2 L
- Determine the obligate fluid intake (approximately 1.5 L)
- Measure weight daily
- Daily water intake = obligate volume + (target weight – daily weight)
- Check plasma sodium weekly
- Educate patients and their family about the principle of the treatment regime
(NPV) of 95%. The performance of the test was better when performed <12 hours after surgery with lower accuracy beyond 24 hours. Similarly, the test proved superior in predicting persistent rather than transient DI (68% versus 32%). Another study of eight out of 58 patients with CDI with a standardised copeptin testing time showed that a peak copeptin level of <12.8 pmol/l at 60 minutes post-extubation predicted CDI, while permanent CDI was excluded with 100% NPV in those with a level of >4.2 pmol/L.53 Interestingly, there was no significant difference in the copeptin level between the two groups in the subsequent post-extubation assessments at 6–48 hours.

Copeptin is a promising marker that will likely be a routine diagnostic test in the evaluation of CDI in the future. However, presently, the number of studies about copeptin use, the uncertainty about the optimal time of its measurement after surgery and the limited availability of the assay are factors limiting its widespread use. Table 1 summarises the various parameters that are frequently needed to be evaluated in post-pituitary-surgery patients and the expected changes in these parameters in patients with postoperative DI. A risk-based algorithm is proposed on the frequency of laboratory investigation to identify DI in the postoperative period [Figure 1].

TREATMENT
Although ADH secretion impairment and the disturbance of fluid balance often begin during the intraoperative period, CDI usually presents within a few hours after surgery. It is imperative to rule out intraoperative fluid overload and glycosuria as potential causes of polyuria. It is also noteworthy that patients with acromegaly may experience increased urinary output following the resection of their pituitary mass due to diuresis of excess fluid within the soft tissues.54,55 Furthermore, approximately 50% and 80% of patients with transient DI recover within seven and 90 days of surgery, respectively.56 As such, patients are advised to monitor for the cessation of thirst sensation and resolution of polyuria as potential signs of DI recovery. Moreover, periodic monitoring of electrolytes can be useful to confirm DI recovery, as water deprivation tests are not routinely recommended in this situation.57 An additional advice is to delay desmopressin (DDAVP) dose for a few hours to see if increased thirst and polyuria persist.53

Patients require continuous monitoring of fluid intake and urine output and frequent assessment of electrolyte. DDAVP should be used cautiously as required, especially during the first two weeks postoperatively to avoid hyponatremia due to overreplacement.54 Treatment of postoperative CDI is multifaceted and can be divided into acute or chronic phases, depending on the stage of the disease, to restore osmotic equilibrium. Although specific guidelines related to the management of postoperative DI are unavailable, in the recent past, a disease state review, followed by guidelines on hypopituitarism, was published, offering some guidance to the clinical management.52,58 The general strategies of management of CDI are presented in Table 2. The acute phase management covers the first two phases of the triphasic water dysregulation phenomenon.

Acute Management of Central Diabetes Insipidus

FREE WATER ACCESS
The management is straightforward, provided there is an intact thirst mechanism, i.e. the patient is not receiving fluids for any reason and can drink water at will. Water balance can be achieved under such a situation as long as the patient can consume enough fluids.59,60 Patients with a decreased level of consciousness and impaired thirst mechanisms or those on intravenous (IV) fluids will require continuous adjustment of IV fluids and pharmacotherapy to maintain adequate hydration and sodium equilibrium. The appearance of hypernatremia and polyuria along with dehydration heralds the onset of CDI. It should be aggressively sought out during the immediate postoperative period as hypernatremia can cause brain shrinkage, leading to vascular rupture and intracranial bleeding, along with other complications.61

The serum sodium level can be normalised safely at a correction rate of 1 mEq/L/h without any untoward complications.59,61 Hypotonic fluids should be used when intravenous fluids are mandated. The least amount of fluid possible should be used and rapid overcorrection must be avoided as it can lead to cerebral edema.61

VASOPRESSIN
Vasopressin is available as an aqueous solution. Due to its short half-life of around 20 minutes, it should be administered through IV infusion when acute control of antidiuresis is needed.64 Infusion is usually started at a rate of 0.25–1.0 micro unit/kg/h and titrated every half hour after that to maintain the urine output rate at around 100 mL/h and/or urine specific gravity at around 1.010–1.020.

DESMOPRESSIN
DDAVP (1-deamino-8-D-arginine vasopressin) is a synthetic analogue of vasopressin, having a prolonged
action profile with minimal vasopressor activity. It can be administered orally, intranasally, subcutaneously or intravenously. Studies have shown a definite relationship between the magnitude and duration of its therapeutic effect and its IV dosage. In patients with CDI, 1 µg IV ‘push’ infusion can increase urine osmolality to a maximum of 700–800 mOsmol/kg. Further increase in dose, from 1 to 8 µg led to prolongation of the duration of action from around 26 hours to 46 hours. The magnitude and duration of its therapeutic effects showed large interindividual variability attributed to individual differences in renal concentration abilities, as it persisted even when the dose was increased to more than 2 µg.

Further studies have shown that the antidiuretic efficacy depends on the total dose as well as the rate of increase in plasma DDAVP level. The human kidney loses concentrating capacity in the absence of vasopressin. Therefore, once treatment is initiated, it requires at least eight hours of continued therapy for full recovery. According to several studies, the parenteral DDAVP can be administered safely to acutely ill patients with CDI. However, the needed dose depends on the individual response, intactness of thirst mechanism and other factors determining fluid intake. In patients with intact thirst mechanisms, a starting dose of 0.25–0.50 µg twice daily as an IV infusion over two hours is usually administered, which is adjusted further to normalise urine output and maintain sodium equilibrium. A smaller dose of 0.06–0.125 µg is usually preferred with further titration to the desired effects for patients who are unable to drink at will or are on IV fluids. Although hyponatremia can be a manifestation of excessive DDAVP administration, the second phase of the triphasic water dysregulation phenomenon also presents with hyponatremia. Both of these have the same underlying mechanism and management principles that require withholding DDAVP along with careful electrolyte and fluid balance monitoring.

CHRONIC MANAGEMENT OF CENTRAL DIABETES INSIPIDUS

Since CDI rarely remits once established, it requires continuous, complete and around-the-clock management of the polyuria and maintenance of sodium and water equilibrium. Hypernatremia rarely goes unnoticed as it is always associated with polyuria and dehydration. Management principles of hypernatremia are same as mentioned above; however, in case the duration of hypernatremia cannot be ascertained, the sodium level should be corrected at a rate of 0.5 mEq/L/h, with no more than an 8–10 mEq/L decrease over 24 hours, while keeping the target sodium level at 145 mEq/L.

Minimising the risk of hyponatremia due to excessive water retention is another critical challenge as it can be occasionally symptomatic and, rarely, life-threatening. Excessive fluid consumption suppresses vasopressin secretion in normal subjects by non-osmotic mechanisms, leading to diuresis and thus preventing over-hydration. This ‘escape’ mechanism is not possible in patients with CDI as they are on exogenous long-acting desmopressin. Consequently, dilutional hyponatremia occurs. A longer-acting form of antidiuretic therapy and limiting fluid intake to the amounts required to satisfy thirst are the possible ways to achieve this goal. Titration of antidiuretic dose to keep 24 hours urine output within the normal range (15–30 mL/kg/day) is equally important.

DESMPRESSIN – NASAL SPRAY

Intranasal DDAVP has an absorption ratio of around 10–20% when compared to IV preparation in patients with CDI. Moreover, it has interindividual and intraindividual variability in the magnitude and duration of its antidiuretic effect. The variability is irrespective of age, severity of polyuria or body-weight, leading to the duration of action ranging from 4–18 hours to 8–24 hours seen with 5–10 and 20 µg, respectively. The intranasal preparation is useful as it allows individualisation of treatment and dose titration by metered-dose spray (2.5–10 µg per spray). One must note that the absorption of nasal DDAVP may be decreased in the setting of nasal inflammation and rhinorrhea, such as in upper respiratory tract infections, and therefore patients may need to use extra doses or shift to other routes if polyuria and dehydration are present.

DESMPRESSIN ORAL TABLETS

Due to their large molecular size and susceptibility to enzymatic degradation coupled with short plasma half-life, vasopressin and DDAVP were initially considered to be unsuitable for oral use. However, despite low oral bioavailability of around 16%, a stable antidiuretic effect with a clear dose–response relationship has been observed in clinical trials, and preparation strengths (0.1, 0.2 and 0.4 mg) are available for oral use. DDAVP oral doses required for equivalent antidiuretic efficacy are around 10–20 times of the intranasal doses; however, the ease of administration makes oral formulations the preferred route of treatment for most patients. Although individualisation of therapy and titration of the dose is needed, 0.1–0.2 mg every eight hours is the usual maintenance dose, while less frequent dosing, such as once or twice daily, is generally sufficient for infants and children.
Management of Diabetes Insipidus following Surgery for Pituitary and Suprasellar Tumours

DESMOPRESSIN ORAL FORMULATIONS – ORAL MELT

Since 2005, DDAVP has been available as a sublingual lyophilizate (Melt) formulation containing 60, 120 and 240 µg, having bioavailability of around 25%. In a recent study, DDAVP Melt has shown a similar level of antidiuretic control and was found to be as efficacious as intranasal DDAVP in both children and adults.

Central Diabetes Insipidus in Specific Populations

NEONATAL INFANTS/CHILDREN

The treatment of CDI in this group requires consideration of their diets which contain a proportionally larger amount of water. Therefore, to prevent hyponatremia, urine volume must not be reduced too much and careful dose titration with close input/output and plasma sodium monitoring are required. Continuous intravenous infusion of low dose DDAVP (0.1–0.2 µg s.c./i.m) or arginine ADH (0.25–3 mU/kg/h) under intensive monitoring is often used in the first 24–48 hours postoperatively. Once CDI is stable and permanent, regular DDAVP can be prescribed. A diluted rhinyl preparation of nasal spray in the amount containing 1–5 µg of DDAVP once or twice daily usually provides good control of CDI in infants.

DDAVP can be administered subcutaneously in doses ranging from 0.02 to 0.08 µg once or twice daily. Children and their parents need to be educated about the features of water intoxication and the hazards of excessive fluid intake.

PREGNANCY AND LACTATION

DDAVP, being resistant to placental leucine aminopeptidase, can be administered safely to pregnant women, both for gestational DI as well as to patients with pre-existing CDI who become pregnant. Compared to non-pregnant women, the doses needed are usually the same or slightly higher. Placental leucine aminopeptidase usually disappears in 4–6 postpartum weeks when DDAVP can be discontinued in patients with gestational DI. It should be kept in mind during the monitoring of therapeutic effects that serum sodium level during pregnancy decreases typically by approximately 5 mmol/L compared to the nongravid state. As DDAVP appears in an infinitesimal amount in breast milk, it can be continued during lactation.

ELDERLY

As mentioned above, CDI requires lifelong management and, even if the underlying cause is eliminated, CDI once established rarely remits. The treatment of CDI in the elderly does not differ much from that in young adults, though the former faces a higher risk of developing hyponatremia, primarily when intranasal DDAVP is used. The aetiology is not clear at present. Abnormalities of osmoregulation of thirst and fluid intake, along with increased renal sensitivity to DDAVP, may be the possible explanation as this population is known to be affected by these factors.

HYPODIPSIA/ADIPSI A WITH CENTRAL DIABETES INSIPIDUS

Anterior hypothalamus injury leading to osmoreceptor damage culminates in the absence or deficiency of thirst and results in the rare occurrence of adipsic DI. As a result, these patients have neither of the homeostatic mechanisms required for water balance regulation. Consequently, their management becomes difficult and they suffer from wide fluctuation in serum sodium levels. In addition, during acute illnesses, patients can develop life-threatening hypernatremia, resulting in somnolence, seizures, hemiplegia, coma and acute renal failure and can experience thrombotic episodes. Furthermore, other complications such as obesity and sleep apnoea, which is largely attributed to hypothalamic abnormalities, may be seen in association with adipsic DI; these conditions contribute to the excess morbidity and mortality found in a patient with adipsic DI. It becomes necessary to prescribe fluid intake on a sliding scale based on daily weight and serum sodium level. DDAVP, alone or in combination with hydrochlorothiazide, is a useful agent in this regard.

An alternative and more practical approach is to set a target weight (kg) at which the patient is known to be euvoletic and normonatremic and maintain fixed urine output at 1.5–2 L with a fixed amount of DDAVP. Furthermore, daily fluid intake can be titrated as obligate load (1.5 L in temperate climates) + (target weight – daily weight) to maintain volume status, sodium and osmolality within the defined range. Successful treatment can be achieved through daily measurement of body weight and perhaps weekly serum sodium measurement along with careful monitoring and patient and family education. Additionally, due to the high rates of venous thrombosis and thromboembolism in patients with adipsic DI, giving low-molecular-weight heparin during periods of hypernatremia dehydration is recommended. Furthermore, screening for sleep abnormalities is indicated. The principles of management of adipsic DI are displayed in Table 3.
Conclusion

CDI is a frequent complication that occurs in patients who undergo surgery for pituitary and suprasellar tumours and is the commonest leading cause for hospital readmission of these patients. Therefore, clinicians dealing with these patients need to perform a thorough preoperative risk assessment in order to identify known predictive factors for CDI, such as in patients with craniopharyngioma and with larger tumours, in order to have clear strategies in place for early diagnosis and management. Moreover, postoperative evaluation should be performed in the early and late postoperative periods in order to reduce the risk of complications and unnecessary readmissions to the hospital. While the management of CDI which complicates surgery for pituitary and suprasellar tumours is a commonly encountered topic, it nonetheless remains a challenging area for clinicians and requires high standards of medical knowledge in tandem with superior clinical experience and skills, especially regarding the decision about when to start desmopressin therapy and for how long, as well as planning the long-term follow-up for those who develop permanent CDI.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FUNDING

No funding was received for this study.

AUTHORS’ CONTRIBUTION

MHA contributed to study design. All authors contributed to the literature review and data collection. All authors drafted the initial manuscript. MHA, MMA, and IB edited the manuscript. MA, KMD, MM and SAB made critical revision and approved final version. All authors reviewed and approved the final version of the manuscript.

References

1. Ezzat S, Issa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, et al. The prevalence of pituitary adenomas: A systematic review. Cancer 2004; 101:613–19. https://doi.org/10.1002/cncr.20412.
2. Hensen J, Henig A, Falhabusch R, Meyer M, Boehnert M, Bachfelder M. Prevalence, predictors and patterns of postoperative polyuria and hyponatraemia in the immediate course after trans-sphenoidal surgery for pituitary adenomas. Clin Endocrinol (Oxf) 1999; 50:431–9. https://doi.org/10.1111/j.1365-2265.1999.00666.x.
3. Blair ET, Clemmer JS, Harkey HL, Hester RL, Pruett WA. Physiologic mechanisms of water and electrolyte disturbances after transsphenoidal pituitary surgery. World Neurosurg 2017; 107:429–36. https://doi.org/10.1016/j.wneu.2017.07.175.
4. Thompson CJ. Polyuric states in man. Bullrises Clin Endocrinol Metab 1989:3473–97. https://doi.org/10.1016/a9050-351x(89)80012-6.
5. Smith D, McKenna K, Moore K, Tormey W, Finucane J, Phillips J, et al. Baroregulation of vasopressin release in adipsic diabetes insipidus. J Clin Endocrinol Metab 2002; 87:4564–8. https://doi.org/10.1210/jc.2002-000990.
6. Sherlock M, Agha A, Crowley K, Smith D, Thompson CJ. Adipsic diabetes insipidus following pituitary surgery for a macroadenoma. Pituitary 2006; 9:29–64. https://doi.org/10.1007/s11202-006-8280-x.
7. Szinnai G, Morgenthaler NG, Bernes K, Struck J, Muller B, Kellner U et al. Changes in plasma copeptin, the c-terminal portion of arginine vasopressin during water deprivation and excess in healthy subjects. J Clin Endocrinol Metab 2007; 92:3973–8. https://doi.org/10.1210/jc.2007-0332.
8. Balanescu S, Kopp P, Gaskill MB, Morgenthaler NG, Schindler C, Rutishauser J. Correlation of plasma copeptin and vasopressin concentrations in hypo-, iso-, and hyperosmolar states. J Clin Endocrinol Metab 2011; 96:1046–52. https://doi.org/10.1210/jc.2010-2499.
9. Katan M, Morgenthaler NG, DIXIT KC, Rutishauser J, Brabant G, Muller B, et al. Anterior and posterior pituitary function testing with simultaneous insulin tolerance test and a novel copeptin assay. J Clin Endocrinol Metab 2007; 92:2640–3. https://doi.org/10.1210/jc.2006-2046.
10. Winzeber C, Zweifel C, Nigro N, Arici B, Bally M, Schuetz P, et al. Postoperative copeptin concentration predicts diabetes insipidus after pituitary surgery. J Clin Endocrinol Metab 2015; 100:2275–82. https://doi.org/10.1210/jc.2014-4527.
11. Baldeweg SE, Ball S, Brooke A, Gleeson HK, Levy MJ, Prentice M, et al. Inpatient management of cranial diabetes insipidus. Endocr Connect 2018; 7:G8–11. https://doi.org/10.1530/EC-18-0154.
12. Sheehan JM, Sheehan JP, Douds GL, Page BB. DDACP use in patients undergoing transsphenoidal surgery for pituitary adenomas. Acta Neurochir (Wien) 2006; 148:287–91. https://doi.org/10.1007/s00701-005-0686-0.
13. Goudakos JK, Markou KD, Georgalas C. Endoscopic versus microscopic trans-sphenoidal pituitary surgery: A systematic review and metaanalysis. Clin Otolaryngol 2011; 36:212–20. https://doi.org/10.1111/j.1749-4486.2011.02331.x.
14. Little AS, Kelly DE, White WL, Gardner PA, Fernandez-Miranda JC, Chicoine MR, et al. Results of a prospective multicenter controlled study comparing surgical outcomes of microscopic versus fully endoscopic transsphenoidal surgery for nonfunctioning pituitary adenomas: The Transsphenoidal Extent of Resection (TRANSsPHER) study. J Neurosurg 2019; 132:1034–53. https://doi.org/10.3171/2018.11.JNS181238.
15. Agam MS, Wedenmeyer MA, Wrobel B, Weiss MH, Carmichael JD. Zada G. Complications associated with microscopic and endoscopic transsphenoidal pituitary surgery: Experience of 1153 consecutive cases treated at a single tertiary care pituitary center. J Neurosurg 2018; 130:1756–83. https://doi.org/10.3171/2017.12.JNS172318.
16. Wang S, Li D, Ni M, Jia W, Zhang Q, He J, Jia G. Clinical predictors of diabetes insipidus after transcranial surgery for pituitary adenoma. World Neurosurg 2017; 101:1–10. https://doi.org/10.1016/j.wneu.2017.01.075.
17. Smith D, Finucane F, Phillips J, Baylis PH, Finucane J, Tormey W, et al. Abnormal regulation of thirst and vasopressin secretion following surgery for craniopharyngioma. Clin Endocrinol (Oxf) 2004; 61:273–9. https://doi.org/10.1111/j.1365-2265.2004.02086.x.
18. Agha A, Rogers B, Mylette D, Tafel E, Tormey W, Phillips J, et al. Neuroendocrine dysfunction in the acute phase of traumatic brain injury. Clin Endocrinol (Oxf) 2004; 60:584–91. https://doi.org/10.1111/j.1365-2265.2004.02022.x.
19. Hannon MJ, Crowley RK, Behan LA, O’Sullivan EP, O’Brien MMC, Sherlock M, et al. Acute glucocorticoid deficiency and diabetes insipidus are common after acute traumatic brain injury and predict mortality. J Clin Endocrinol Metab 2013; 98:3229–37. https://doi.org/10.1210/jc.2013-1555.
20. Qureshi AI, Suri MF, Sung GY, Straw R, Yahia AM, Saad M, et al. Prognostic significance of hypernatremia and hyponatremia among patients with aneurysmal subarachnoid hemorrhage. Neurosurgery 2002; 50:749–56. https://doi.org/10.1093/neuros/21-23/2000400-00012.
21. Barker FG 2nd, Klabanski A; Swearingen B. Transsphenoidal surgery for pituitary tumours in the United States, 1996-2000: Mortality, morbidity, and the effects of hospital and surgeon volume. J Clin Endocrinol Metab 2003; 88:4709–19. https://doi.org/10.1210/jc.2003-03461.
22. Ajan AM, Abdulqader SB, Achrol AS, Aljaaman Y, Feroze AH, Katzenelson L, et al. Diabetes insipidus following endoscopic transsphenoidal surgery for pituitary adenoma. J Neurol Surg B Skull Base 2018; 79:117–22. https://doi.org/10.1055/s-0036-1604363.
23. Sigounas D, Sharpless J, Cheng D, Johnson T, Senior B, Ewend M. Predictors and incidence of central diabetes insipidus after endoscopic pituitary surgery. Neurosurgery 2008; 62:71–8. https://doi.org/10.1227/01.NEU.0000311063.10745.D8.
24. Nemergut EC, Zuo Z, Jane Jr JA, Laws Jr ER. Predictors of diabetes insipidus following transsphenoidal surgery: A review of 881 patients. J Neurosurg 2005; 103:448–54. https://doi.org/10.3171/jns.2005.103.3.0448.
25. Pratheesh R, Swallow DMA, Rajaratnam S, Joseph M, et al. Incidence, predictors and early postoperative course of diabetes insipidus in pediatric craniopharyngioma: A comparison with adults. Child's Nerv Syst 2013; 29:941–9. https://doi.org/10.1007/s00381-013-1041-8.
26. Kristof RA, Rother M, Neuloh G, Klingmüller D. Incidence, clinical manifestations, and course of water and electrolyte metabolism disturbances following transsphenoidal pituitary adenoma surgery: A prospective observational study. J Neurosurg 2009; 111:555–62. https://doi.org/10.3171/2009.8.JNS08191.
27. Prete A, Corsello SM, Salvatori R. Current best practice in the management of patients after pituitary surgery. Ther Adv Endo- crinol Metab 2017; 8:33–48. https://doi.org/10.1177/1758828816687240.
28. Wedemeyer MA, Lin M, Fredrickson VL, Arakelyan A, Bradley D, Donoho DA, et al. Recurrent Rathke's cleft cysts: Incidence and surgical management in a tertiary pituitary center over 2 decades. Oper Neurosurg (Hagerstown) 2018; 16:675–84. https://doi.org/10.1093/ons/qyx258.
29. Hayashi Y, Aida Y, Sasagawa Y, Oishi M, Kita D, Tachibana O, et al. Delayed occurrence of diabetes insipidus after transphenoidal surgery with radiologic evaluation of the pituitary stalk on magnetic resonance imaging. World Neurosurg 2018; 110:e1072–7. https://doi.org/10.1016/j.wneu.2017.11.169.
30. Schreckinger M, Walker B, Knepper J, Hornyak M, Hong D, Kim Jung-Min, et al. Delayed occurrence of diabetes insipidus after transsphenoidal surgery. Pituitary 2013; 16:445–51. https://doi.org/10.1007/s11122-012-0453-1.
31. Yuen KCJ, Ajmal A, Correa R, Little AS, Sodium perturbations after pituitary surgery. Neurosurg Clin N Am 2019; 30:515–24. https://doi.org/10.1016/j.nec.2019.05.011.
32. Hoon EJ, Zietse R. Water balance disorders after neurosurgery: The triphasic response revisited. NDT Plus 2010; 3:42–4. https://doi.org/10.1093/ndtplus/sfp117.
33. Loh JA, Verbalis JG. Diabetes insipidus as a complication after pituitary surgery. Nat Clin Pract Endocrinol Metab 2007; 3:489–94. https://doi.org/10.1038/ncpe2005013.
34. Seckel J, Dunger D. Postoperative diabetes insipidus. BMJ 1989; 298:2–3. https://doi.org/10.1136/bmj.298.6665.2.
35. Hans P, Stevens A, Albert A. Study of hypotonic polyuria after trans-sphenoidal pituitary adenectomy. Intensive Care Med 1986; 12:95–9. https://doi.org/10.1007/BF00254519.
36. Fanske W, Allolio B. Current state and future perspectives in the diagnosis of diabetes insipidus: A clinical review. J Clin Endo- crinol 2012; 97:3426–37. https://doi.org/10.1210/jc.2012-1981.
54. Sheehan JM, Sheehan JP, Douds GL, Page RB. DDAVP use in patients undergoing transphenoidal surgery for pituitary adenomas. Acta Neurochir 2006; 148:287–91. https://doi.org/10.1007/s00701-005-0686-0.

55. Adams JR, Belvins LS, Allen GS, Verity DK, Devin JK. Disorders of water metabolism following transphenoidal pituitary surgery: a single institution’s experience. Pituitary 2006; 9:93–9. https://doi.org/10.1007/s11125-006-9276-2.

56. Adams JR, Belvins Jr LS, Verity DK, Devin JK. Disorders of water metabolism following transphenoidal pituitary surgery: A single institution’s experience. Pituitary 2006; 9:93–9. https://doi.org/10.1007/s11125-006-9276-2.

57. Garraby A, Moran C, Thompson CJ. Diagnosis and management of central diabetes insipidus in adults. Clin Endocrinol (Oxf) 2019; 90:23–30. https://doi.org/10.1111/cen.13866.

58. Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, et al. Hypothalamic replacement in hypopituitarism in adults: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2016; 101:3888–92. https://doi.org/10.1210/jc.2016-2118.

59. Dumont AS, Nemergut EC, Jane Jr JA, Laws Jr ER. Postoperative care following pituitary surgery. J Intensive Care Med 2005; 20:127–40. https://doi.org/10.1177/1054143905275247.

60. Makaryus AN, McFarlane SI. Diabetes insipidus: Diagnosis and treatment of a complex disease. Cleve Clin J Med 2006; 73:65–71. https://doi.org/10.3949/ccjm.73.1.65.

61. Adrogue HJ, Madrias NE. Hypernatremia. N Engl J Med 2000; 342:1493–9. https://doi.org/10.1056/NEJM200005183420606.

62. Pfennig CL, Slovis CM. Sodium disorders in the emergency department: A review of hyponatremia and hypernatremia. Emerg Med Pract 2012; 14:1–26. PMID: 23114652.

63. Reynolds RM, Padfield P, Seckl JR. Disorders of sodium balance. BMJ 2006; 332:702–5. https://doi.org/10.1136/bmj.332.7354.702.

64. Chanson P, Jendrayk CP, Dabrowski G, Rohan J, Bouchama A, Rohan-Chabot P, et al. Ultralow doses of vasopressin in the management of diabetes insipidus. Crit Care Med 1987; 15:44–6. https://doi.org/10.1097/00003246-198701000-00010.

65. Andersson KE, Arner B. Effects of DDAVP, a synthentic analogue of vasopressin, in patients with cranial diabetes insipidus. Acta Med Scand 1972; 192:21–7. https://doi.org/10.1111/j.0954-6820.1972.tb04772.x.

66. Radó JP, Marosi J, Szender I, Borbély L, Takó J, Fischer J. The antidiuretic action of 1-deamino-8-D-arginine vasopressin (DDAVP) in man. Int J Clin Pharmacol Biopharm 1976; 13:199–209.

67. Radó JP, Marosi J, Fischer J, Takó J, Kiss N. Relationship between the dose of 1-deamino-8-D-arginine vasopressin (DDAVP) and antidiuretic response in man. Endocrinology 1975; 66:184–195.

68. Radó JP, Marosi J, Borbély L, Takó J. Individual differences in the antidiuretic response induced by single doses of 1-deamino-8-D-arginine-vasopressin (DDAVP) in patients with pituitary diabetes insipidus. Int J Clin Pharmacol Biopharm 1976; 14:259–65.

69. Czakó L, Mezei G, László FA. Treatment of diabetes insipidus. Endocrine Pract 2011; 17:467–74. https://doi.org/10.1007/s12020-011-9492-2.

70. Zerbe RL, Robertson GL. A comparison of plasma vasopressin measurements with a standard indirect test in the differential diagnosis of polyuria. N Engl J Med 1981; 305:1539–46. https://doi.org/10.1056/NEJM198112243052601.

71. Kahn A, Bracht E, Blum D. Controlled fall in natriemia and risk of seizures in hypertonic dehydration. Intensive Care Med 1979; 5:27–31. https://doi.org/10.1007/BF01738999.

72. Thomas CJ, Burd JM, Baylis PH. Acute suppression of plasma vasopressin and thirst after drinking in hypotermic humans. Am J Physiol 1987; 252:R1138–42. https://doi.org/10.1152/ajpregu.1987.252.6.R1138.

73. Seckel JR, Williams TD, Lightman SL. Oral hypertonic saline causes transient fall of vasopressin in humans. Am J Physiol 1986; 251:R214–17. https://doi.org/10.1152/ajpregu.1986.251.2.R214.

74. Kovacs L, Rittig S, Robertson GL. Effect of sustained antidiuretic treatment on plasma sodium concentration and body water homeostasis in healthy humans on ad libitum fluid intake. Clin Res 1992; 40:165A.

75. Andersson KE, Arner B. Effects of DDAVP, a synthentic analogue of vasopressin, in patients with crinarian diabetes insipidus. Acta Med Scand 1972; 192:21–7. https://doi.org/10.1111/j.0954-6820.1972.tb04772.x.

76. Aronson AS, Andersson KE, Bergstrand CG, Mulder JL. Treatment of diabetes insipidus in children with DDAVP, a synthentic analogue of vasopressin. Acta Pediatr Scand 1973; 62:133–40. https://doi.org/10.1111/j.1651-2277.1973.tb08080.x.

77. Becker DJ, Foley TP. Jr.1-Deamino-8-D-arginine-vasopressin in the treatment of central diabetes insipidus in childhood. J Pediatr 1978; 92:1011–15. https://doi.org/10.1016/s0022-3476(78)80389-8.

78. Robinson AG. DDAVP in the treatment of central diabetes insipidus. N Engl J Med 1976; 294:507–11. https://doi.org/10.1056/NEJM197603092941001.

79. Ward MK, Fraser TR. DDAVP in treatment of vasopressin-sensitive diabetes insipidus. Br Med J 1974; 3:386–9. https://doi.org/10.1136/bmj.3.5923.86.

80. Fjelasted-Paulsen A, Höglund P, Lundin S, Paulsen O. Pharamacokinetics of 1-deamino-8-D-argininevasopressin after various routes of administration in health volunteers. Clin Endocrinol (Oxf) 1993; 38:177–82. https://doi.org/10.1111/j.1365-2265.1993.tb00990.x.

81. Westgren U, Wittström C, Harris AS. Oral desmopressin in central diabetes insipidus. Arch Dis Child 1986; 61:247–50. https://doi.org/10.1136/adc.61.3.247.

82. Rivkees SA, Dunbar N, Wilson TA. The management of central diabetes insipidus in infancy: Desmopressin, low renal salt load formula, thiazide diuretics. J Pediatr Endocrinol Metab 2007; 20:459–69. https://doi.org/10.1515/jpem.2007.20.4.459.

83. Österberg O, Balchen T, Riis A, Senderovitz T. Pharmacokinetics of desmopressin in children and adults using a new oral lyophilisate. Arch Dis Child 2006; 91:A33.

84. Arina H, Oso Y, huw KV, Nørgaard JP. Efficacy and safety of desmopressin orally disintegrating tablet in patients with central diabetes insipidus: Results of a multicenter open-label dose- titration study. Endocr 2013; 60:1085–94. https://doi.org/10.1515/endocej.2013-0165.

85. Lehrbrecher T, Muller-Scholden J, Danhauser-Leistner I, Sørensen N, von Stockhausen HB. Perioperative fluid and electrolyte management in children undergoing surgery for craniohypophysis: A 10-year experience in a single institution. Childs Nerv Syst 1998; 14:276–9. https://doi.org/10.1007/s003810050224.

86. McDonald JA, Martha PM, Kerrigan J, Clarke WL, Rogol AD, Blizzard RM. Treatment of the young child with postoperative central diabetes insipidus. Am J Dis Child 1989; 143:201–4. https://doi.org/10.1001/archpedi.1989.02150140095027.

87. Gutmark-Little I, Repaska DR, Backeljaue PF. Efficacy and safety of intranasal desmopressin acetate administered orally for the management of infants with neurogenic diabetes insipidus (DI). Endocrine Rev 2010; 31:3-324.
90. Blanco EJ, Lane AH, Aljaz N, Blumberg D, Wilson TA. Use of subcutaneous DDAVP in infants with central diabetes insipidus. J Pediatr Endocrinol Metab 2006; 19:919–25. https://doi.org/10.1515/jpem.2006.19.7.919.

91. Durr JA, Hoggard JG, Hunt JM, Schrier RW. Diabetes insipidus in pregnancy associated with abnormally high circulating vasopressinase activity. N Engl J Med 1987; 316:1070–4. https://doi.org/10.1056/NEJM198704233161707.

92. Barron WM. Water metabolism and vasopressin secretion during pregnancy. Baillieres Clin Obstet Gynaecol 1987; 1:853–71. https://doi.org/10.1198/0950-3552(87)80038-x.

93. Burrow GN, Wassenaar W, Robertson GL, Sehl H. DDAVP treatment of diabetes insipidus during pregnancy and the postpartum period. Acta Endocrinol (Copenh) 1981; 97:23–5. https://doi.org/10.1530/acta.0.0970023.

94. Czernichow P. Treatment of diabetes insipidus. In: Argente J, Ed. Diabetes Insipidus. Madrid, Spain: Editorial Justim, 2010. Pp. 107–112.

95. Cuesta M, Hannon MJ, Thompson CJ. Adipsic diabetes insipidus in adult patients. Pituitary 2017; 20:372–80. https://doi.org/10.1007/s11102-016-0784-4.

96. Milijc D, Milijc P, Doknic M, Pekic S, Stojanovic M, Petakov M, et al. Adipsic diabetes insipidus and venous thromboembolism (VTE): Recommendations for addressing its hypercoagulability. Hormones (Athens) 2014; 13:820–3. https://doi.org/10.14331/horm.2002.1496.

97. Green RP, Landt M. Home sodium monitoring in patients with diabetes insipidus. J Pediatr 2002; 141:618–24. https://doi.org/10.1067/mpd.2002.128544.

98. Ball SG, Vaidja B, Baylis PH. Hypothalamic adipsic syndrome: Diagnosis and management. Clin Endocrinol (Oxf) 1997; 47:405–9. https://doi.org/10.1111/j.1365-2265.1997.2591079.x.

99. Crowley RK, Woods C, Fleming M, Rogers B, Behan LA, O’Sullivan EP, et al. Somnolence in adult craniopharyngioma patients is a common, heterogeneous condition that is potentially treatable. Clin Endocrinol (Oxf) 2011; 74:750–5. https://doi.org/10.1111/j.1365-2265.2011.03993.x.