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Review

Diabetes insipidus following resection of pituitary tumors

Matthew Schreckinger, Nicholas Szerlip, Sandeep Mittal*

Department of Neurosurgery, Wayne State University and Detroit Medical Center, Detroit, MI, United States

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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.

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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

* Corresponding author at: Department of Neurosurgery, Wayne State University, 4160 John R Street, Suite 930, Detroit, MI 48201, United States. Tel.: +1 313 966 0342; fax: +1 313 966 0368.
E-mail address: smittal@med.wayne.edu (S. Mittal).

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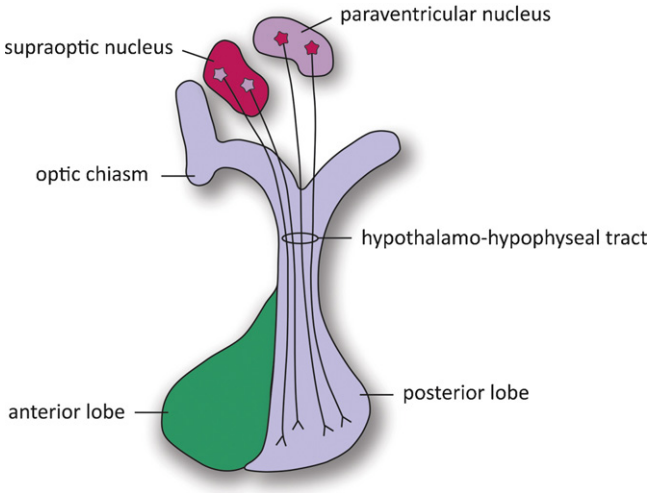

Fig. 1. Arginine vasopressin is produced by magnocellular neurons in the supraoptic and paraventricular nuclei of the hypothalamus and is transported to the neurohypophysis via the hypothalamo–hypophyseal tract. Injury to these structures can lead to transient or permanent DI.

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