Central Diabetes Insipidus (Etiology, Epidemiology, and Management)

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Introduction

Diabetes insipidus (DI) is a heterogeneous disorder that is characterized by the lack of ability to conserve free water and concentrate urine. This results in polyuria and polydipsia, which are the main manifestations of the disease [1].

DI is classified broadly according to its etiology as central or nephrogenic. Central diabetes insipidus (CDI) is due to a deficiency of arginine vasopressin (AVP), which is also called antidiuretic hormone (ADH), whereas nephrogenic DI is due to resistance to ADH action at the collecting tubules of the kidney [2].

AVP is produced and secreted from the neurons of the supraoptic and paraventricular nuclei that are located in the hypothalamus and transported caudally via their axons to the posterior pituitary where it is stored in secretory granules and released. The main stimulus for the release of ADH is serum osmolality, which is detected by the body through delicately sensitive osmoreceptors located within the subfornical organ and the organum vasculosum lamina terminalis, whose neurons transmit signals to supraoptic neurons that respond to variations in osmotic pressure as low as two mOsm/L. ADH is also regulated by hypovolemia, which is sensed through baroreceptors located in the carotid artery, aortic arch, and left atrium that transmit information to the vagus nerve, directly stimulating the secretion of ADH. When AVP is released into the circulation, it acts on the distal convoluted tubule (DCT) and the collecting duct (CD) to absorb free water by stimulating the insertion of Aquaporin-2 channels in the apical membrane of the DCT and CD cells, allowing water to move down its concentration gradient back into the vasculature. A secondary response to a rising serum osmolality is thirst, which is a powerful physiologic mechanism designed to increase water intake. Thus, under normal circumstances, ADH and thirst act in concert to ensure that salt and water balance remains normal [3–5].

In the absence of AVP, free water is lost through the renal collecting system resulting in extreme polyuria, polydipsia, and dilute urine. In a child with an intact thirst mechanism and free access to water, serum sodium and osmolality remain normal at the expense of excessive drinking. Therefore, the body must be challenged through a "water deprivation test" in order to confirm a diagnosis of DI (see Chaps. 17 and 28).

Etiology

Any impairment in ADH production or secretion can result in CDI, which can be congenital or acquired (Fig. 55.1). A number of known genetic etiologies of CDI also exist, which may be transmitted according to a variety of inheritance patterns or arise de novo [6].

Epidemiology

CDI is rare in the pediatric population. According to a large Danish study, the incidence is 3–4 per 100,000 with a higher ratio in boys than in girls [7, 8]. Complaints of polydipsia and polyuria are extremely common in pediatric patients, particularly during the toddler years, but the majority of children with polydipsia and polyuria do not have CDI. Important elements of the history include the quantity of fluid intake, what the preferred beverage is, and whether the excessive drinking and urination also occur at night. Findings that increase the likelihood of CDI include older age, higher baseline serum sodium and osmolality, and a propensity for inappropriate water-seeking behavior such as

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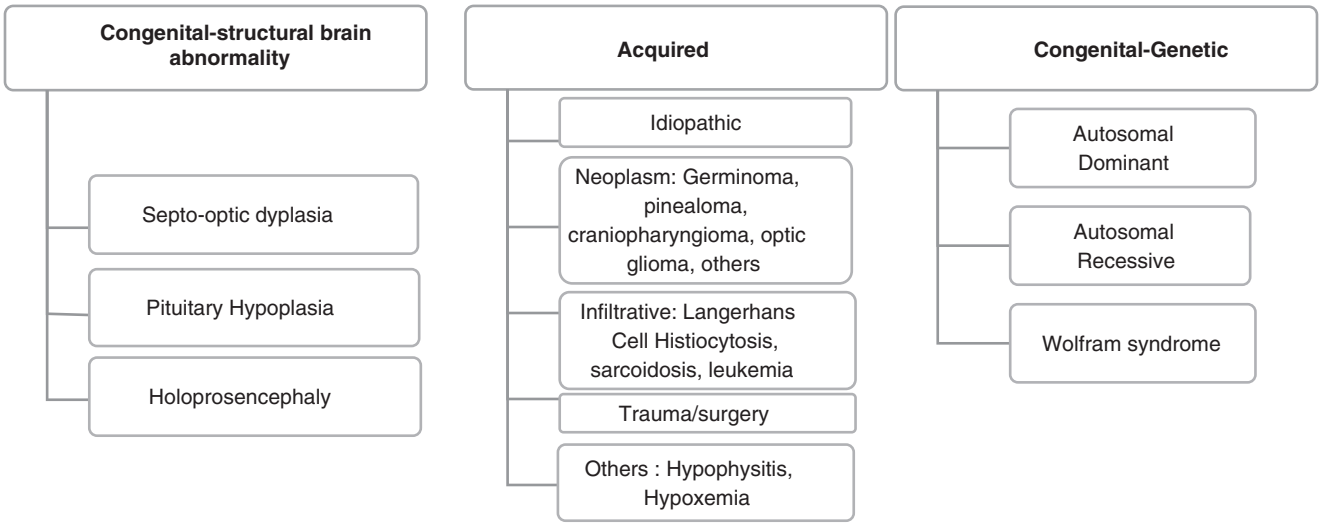

Fig. 55.1 Etiologic categories of CDI along with their differential diagnoses

drinking out of faucets, birdbaths, fountains, and flower vases [9]. Table 55.1 summarizes clinical features consistent with a diagnosis of CDI.

Reference Box: Key Pathophysiology

- Central diabetes insipidus results from injury to or absence of the AVP-secreting neurons located in the paraventricular and supraoptic nuclei of the hypothalamus, resulting in decreased AVP production.
- The consequence of inadequate AVP production or secretion is the inability to concentrate urine.
- Increased polyuria and polydipsia lead to hypernatremia, high serum osmolality, and inappropriately low urine osmolality and specific gravity when water is withheld.

Urgent or Emergent Considerations and Initial Management

DI can be a life-threatening condition when the body's compensatory mechanisms are inadequate such as in children without an intact thirst or in those with no access to water. Particularly vulnerable patients include infants and neurologically impaired children.

The initial management of CDI depends on the severity of the biochemical abnormalities and the clinical situation. In patients presenting with significant hypernatremia, hospitalization in an intensive care unit is required. The free water

Table 55.1 Items required for diagnosis and items supporting diagnosis

	For diagnosis	Supporting diagnosis
History	Polyuria Polydipsia	New-onset enuresis Irritability Dehydration Symptoms of underlying etiology, such as growth deceleration, fatigue, visual changes, headache, and vomiting Family history of CDI Known diagnosis of hypopituitarism
Examination		Visual field deficits Signs of dehydration Failure to thrive
Laboratory tests	Inappropriately dilute urine in the setting of increased serum osmolality	Tests for hypopituitarism
Imaging		Brain MRI: Thickened pituitary stalk Absence of the posterior pituitary bright spot[a] Ectopic posterior pituitary Structural abnormality or intracranial tumor
Genetic		Confirmed mutation in the gene encoding for AVP or its carrier protein, neurophysin II or in genes implicated in Wolfram syndrome

[a]Lack of a posterior pituitary bright spot can be seen a subset of normal individuals and may also be seen in nephrogenic diabetes insipidus

deficit can be calculated using the following formula: [desired decrease in serum sodium (mEq/L) × weight in kg × 4]. It is always safer to aim for a higher serum sodium due to concerns of rapid correction of hypernatremia, which can lead to cerebral edema and cause permanent brain damage. Therefore, targeting serum sodium to the mid-140s is appropriate. The rate of correction of serum sodium depends on the chronicity of the hypernatremia. When this is unknown, a very slow rate of 0.5 mEq/L per hour drop in serum sodium is recommended (no more than 12 mEq/L/day). When laboratory data are consistent with DI, a test dose of AVP or DDAVP is administered. If this is followed by decreased urine output and an increase in urine osmolality and specific gravity, the diagnosis of CDI is confirmed. In children presenting with CDI without a known CNS abnormality, a brain MRI scan is mandatory due to concerns about an intracranial neoplasm or Langerhans cell histiocytosis (see Fig. 55.1).

Chronic Management and Considerations for Referral

All patients with CDI should be referred to a pediatric endocrinologist for ongoing management and follow-up regardless of the etiology. In neurologically normal children, the therapeutic aims of treatment are mainly to decrease polyuria and thirst in order to improve the quality of life and allow for normal growth. The mainstay of treatment in CDI is DDAVP, which is a synthetic analog of endogenous AVP that has a 2000- to 3000-fold lower vasopressor effect. It is available in oral, intranasal, and parenteral forms that differ in potency by a factor of 10. For example, 1 mcg of SQ DDAVP is equal to 10 mcg of intranasal DDAVP, which is equal to 100 mcg of oral DDAVP. Thus, exquisite care must be taken by prescribers and pharmacists to ensure that inadvertent errors in dosing do not occur. The vast majority of children with CDI are treated with DDAVP tablets which come in a 0.1 mg and 0.2 mg strength. However, there is extensive individual variation in DDAVP dose requirements among patients with CDI. At our center, we have observed that children with acquired etiologies of CDI are more likely to require higher doses of DDAVP (≥1 mg per day) than those with congenital causes. The greatest concern with the use of DDAVP is the potential for hyponatremia [10]. This is related to the fact that DDAVP exerts its effect through an "all or none" phenomenon. Once onboard, essentially all water ingested will be conserved by the body until the drug has been metabolized. Therefore, parents are counseled about the importance of waiting until they observe "breakthrough," i.e., diuresis and increased thirst in their child, prior to each dose. A concern for inadvertent hyponatremia also underlies concerns around prescribing DDAVP for nocturnal enuresis in otherwise healthy children. Indeed, this practice has been linked to several tragic cases of brain herniation and death due to excessive fluid intake following the administration of DDAVP [10].

Management of CDI in Special Situations

Infants with CDI

The treatment in this age group is very challenging as they are entirely dependent on administered fluid such as breast milk or formula. Therefore, frequent measurement of serum sodium, especially when starting therapy, is essential in order to minimize the risk of hyponatremia. Thiazide diuretics are preferred by some clinicians as an alternative to DDAVP, although studies have not found these to be more effective [11, 12]. Some endocrinologists have moved toward using intranasal DDAVP preparations in infants with CDI, with the dose administered orally rather than intranasally.

Children with CDI and Lack of an Intact Thirst Mechanism

Effective treatment can be achieved via a fixed daily fluid intake with DDAVP given at doses that allow for appropriate urine output. However, serum sodium tends to fluctuate significantly in children without an intact thirst mechanism. Therefore, they require ongoing monitoring of serum sodium, urine output, and urine specific gravity. Treatment should be initiated in a hospital setting and titrated in order to maintain serum sodium in a "safe" range which is generally from the low 130s to the mid 150s .In neurologically impaired children, free water boluses can be administered per G-tube as needed [13].

Status Postoperative Intracranial Surgery Patients

The management of postoperative CDI can be challenging and fluid balance needs to be closely monitored in an intensive care setting through the assessment of urine output, serum sodium, and urine specific gravity. IV fluids consisting of normal saline along with a continuous intravenous infusion of vasopressin is preferred in the acute setting due to its short duration of action. Children can be transitioned to oral or intranasal DDAVP once they are tolerating a normal PO intake and are otherwise clinically stable [14, 15].

Management of CDI During Chemotherapy

Children who undergo chemotherapy often require excessive fluid therapy, especially when they are administered nephrotoxic chemotherapeutic agents. Hence, it is recommended to hold DDAVP during these periods to avoid the risk of severe hyponatremia. Close monitoring of fluid intake and output, weight, urine specific gravity, and serum sodium levels is required. A vasopressin drip can be started if needed at a very low dose with an initial rate of 0.08–0.10 mU/kg per hour during hydration therapy where it will permit flexible regulation of fluid and electrolyte balance while simultaneously avoiding the risk of giving or holding the DDAVP [16].

Conclusion

CDI is a heterogeneous disorder with a broad differential diagnosis. Its management ranges from the relatively straightforward outpatient care of an otherwise healthy child with an intact thirst mechanism to that of a critically ill child in the intensive care setting, who requires hourly monitoring. An understanding of normal physiology and the mechanism of action of DDAVP will result in optimal outcomes in most cases. Regardless of the clinical setting, a pediatric endocrinologist is an essential part of the treatment team.

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