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Diabetes insipidus in infants and children

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Diabetes insipidus, the inability to concentrate urine resulting in polyuria and polydipsia, can have different manifestations and management considerations in infants and children compared to adults. Central diabetes insipidus, secondary to lack of vasopressin production, is more common in children than is nephrogenic diabetes insipidus, the inability to respond appropriately to vasopressin. The goal of treatment in both forms of diabetes insipidus is to decrease urine output and thirst while allowing for appropriate fluid balance, normonatremia and ensuring an acceptable quality of life for each patient. An infant's obligate need to consume calories as liquid and the need for readjustment of medication dosing in growing children both present unique challenges for diabetes insipidus management in the pediatric population. Treatment modalities typically include vasopressin or thiazide diuretics. Special consideration must be given when managing diabetes insipidus in the adipsic patient, post-surgical patient, and in those undergoing chemotherapy or receiving medications that alter free water clearance.

Epidemiology

Diabetes Insipidus (DI) is characterized by the inability to concentrate urine secondary to vasopressin deficiency or to vasopressin resistance resulting in polyuria. DI is rare, with a prevalence

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estimated at 1:25,000; fewer than 10% of cases are hereditary in nature [1]. Central DI (CDI) accounts for greater than 90% of cases of DI and can present at any age, depending on the cause. No prevalence for hereditary causes of CDI has been established. Nephrogenic DI (NDI) is less frequent than CDI. X-linked NDI (XLNDI) accounts for 90% of cases or 4–8 cases per one million male births, and autosomal recessive NDI accounts for the other 10%.

Pathophysiology and etiologies

DI can be classified as either CDI or NDI. Vasopressin is produced in the magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus which send axons to the posterior pituitary. The posterior pituitary then secretes vasopressin into the bloodstream. In CDI, production or release of vasopressin from these neurons is impaired. In contrast, patients with NDI have normal vasopressin synthesis but absent response to the hormone at the level of the kidney. Vasopressin acts at V2 receptors (V2R) located at the basolateral membrane of the collecting duct of the kidney. Activation of these receptors by vasopressin leads to insertion of aquaporin 2 (AQP2) channels along the apical cell membrane. AQP2 channels allow for the movement of water from the lumen of the collecting duct, through the lining cells of the collecting duct and through the renal medulla into ascending vasa recta which return water to the general circulation. In NDI, defects are more common in the V2R than in the AQP2 channels (Chapter 8); NDI may also be due to medication-induced renal resistance to vasopressin.

Nonheritable etiologies of CDI include developmental abnormalities of the pituitary gland, mechanical destruction by an intracranial tumor, trauma or hypoxic injury causing disruption of supporting blood vessels, pituitary gland infiltration, or pituitary inflammation or infection. Some forms of DI can be transient while others are permanent. A list of etiologies is presented in Table 1.

Heritable forms of CDI can be autosomal dominant or recessive (Chapter 7). The more common autosomal dominant form typically appears after the first year of life as a result of toxic accumulation of vasopressin precursors in the endoplasmic reticulum. The mutant hormone exerts a dominant negative

Table 1
Etiologies of DI.

Congenital	*Acquired*
- Septo Optic Dysplasia	- Idiopathic DI
- Pituitary Hypoplasia	- Intracranial Tumors:
- Holoprosencephaly	◦ Germinoma
Genetic	◦ Pinealoma
- Autosomal Dominant Central DI	◦ Craniopharyngioma
- Wolfram Syndrome (*WFS1*)	◦ Optic Glioma
- X linked Nephrogenic DI	- Infiltrative
- Autosomal Recessive Nephrogenic DI	◦ Langerhans Cell Histiocytosis
Medications (primarily cause NDI)	◦ Sarcoidosis
- Lithium	◦ Leukemia
- Demeclocyline	- Autoimmune Hypophysitis
- Antimicrobials (foscarnet, amphotericin B)	- Infections
- Antineoplastic agents (vinblastine, cisplatin, cyclophosphamide, ifosfamide)	◦ Meningococcal
	◦ Cryptococcal
- Methoxyflurane	◦ Listeria
- Colchicine	◦ Toxoplasmosis
- Sulfonylureas	◦ Meningitis
	◦ Congenital CMV
	- Trauma
	- Electrolyte disturbances
	◦ Hypokalemia
	◦ Hypercalcemia
	- Hypoxic-Ischemic Injury
	- Postpartum Hemorrhage (Sheehan Syndrome)