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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)

effect on normal vasopressin molecules. Autosomal recessive CDI is less common and tends to present within the first 3 months of life, similar to the presentation of NDI [2].

Wolfram syndrome is another inherited form of CDI. It results from a loss-of-function mutation in the *WFS1* gene resulting in a rare and progressive neurodegenerative disease. Classic Wolfram Syndrome Type 1 comprises non-autoimmune diabetes mellitus, optic atrophy, and CDI. The DI associated with Wolfram syndrome can be complete or partial and typically has its onset in adolescence. Wolfram Syndrome Type 2 is less common and has similar clinical features but does not have DI [3,4]. In *post mortem* studies, accumulation of vasopressin precursors in the paraventricular nuclei suggests that the etiology of CDI in these patients is a defect in vasopressin processing or in neuronal migration [5]. Other associated endocrinopathies are hypogonadism, growth hormone deficiency, nonautoimmune hypothyroidism and defective corticotrophin secretion [4,5]. Management of CDI in Wolfram Syndrome follows the same principles as treatment of other etiologies of CDI.

CDI may be an occasional component of septo-optic dysplasia (SOD), a condition characterized by optic nerve hypoplasia, abnormal septum pellucidum, and deficiency of anterior and/or posterior pituitary hormone function [6]. In the setting of SOD, more than 50% of children are reported to have abnormal thirst, a higher percentage of abnormal thirst than with other forms of DI [7].

As mentioned, a number of central nervous system tumors may produce DI. Craniopharyngioma is a relatively common tumor producing CDI in approximately 55% of patients [8]. Craniopharyngioma often presents with the combination of growth failure and DI. Langerhans Cell Histiocytosis (LCH) results in DI in 42% of affected children [9]. Intracranial germinomas are associated with DI in 80% of children [10]. Of note, LCH and germinomas may not be evident on initial pituitary imaging after diagnosis of CDI.

Symptoms and diagnosis

Individuals with DI are polyuric and polydipsic. They exhibit extreme thirst with intense water seeking behaviors and strongly prefer cold water. A small study examining suppression of vasopressin in dehydrated patients given ice chips versus tap water suggested that the cold temperature of ingested liquid may play a role in satiation of thirst and also appears to suppress vasopressin in dehydrated, hyperosmolar patients without DI [11].

Polyuria is defined as one of the following: urine output (UOP) greater than 2 L/m^2/day, 150 ml/kg/day in neonates, 100–110 ml/kg/day in children up to age 2, and 40–50 ml/kg/day in older children [12]. New onset enuresis in previously toilet-trained patients should raise suspicion of DI (or of diabetes mellitus).

In children, DI often presents with additional signs or symptoms due to effects of intracranial neoplasms on brain structures and to effects on other pituitary axes. Growth retardation, fatigue, headache, emesis and visual field deficits have been described as presenting symptoms [13]. Slowed weight gain and linear growth may result from a child's strong preference for water, limiting the intake of more caloric liquids or solids, or from accompanying growth hormone deficiency. Children presenting with any of these signs or symptoms should be evaluated for DI.

Once polyuria is established, laboratory workup should include serum osmolality (S_{osm}), serum sodium, potassium, glucose, calcium, and blood urea nitrogen, urine osmolality (U_{osm}), urine specific gravity, and urine glucose. Normal serum glucose and calcium rule out diabetes mellitus or hypercalcemia-induced NDI as causes of polyuria. Normal serum potassium excludes hypokalemia induced NDI and normal BUN makes intrinsic renal disease less likely. A S_{osm} greater than 300 mOsm/kg at the same time as an inappropriately dilute urine (U_{osm} < 300 mOsm/kg) is indicative of DI.

In contrast, if U_{osm} > 600 mOsm/kg the patient is unlikely to have DI. If levels are indeterminate, such as S_{osm} < 300 with a U_{osm} < 600 and clinical suspicion of DI remains, further work-up is needed.

A water deprivation test is used to confirm the diagnosis of DI and should always be performed in a closely monitored medical setting. It is not recommended to perform water deprivation tests at home. The goal of the test is to observe the patient's urine concentrating ability and to assess the response to vasopressin. The test is usually begun overnight, and the child deprived of all liquids. Baseline weight, pulse, and blood pressure are obtained and followed hourly. Serum sodium, U_{osm}, urine specific gravity,

urine volume and S_{osm} are also obtained hourly. Serum BUN and plasma vasopressin can be obtained at baseline and at the conclusion of the test [12,14,15].

If the patient develops clinical signs of hypovolemia at any point or if the weight loss is >5% of the starting weight, the test should be terminated. If the U_{osm} is > 1000 mOsm/kg once or >600 mOsm/kg and stable (within 30 mOsm/kg) for two consecutive voids, the test is stopped, and the patient does not have DI. If the S_{osm} is > 300 mOsm/kg and the U_{osm} < 600 mOsm/kg, the patient has DI and 1 unit/m^2 subcutaneous vasopressin should be given. UOP and S_{osm} should then be measured. In a patient with CDI, UOP should fall quickly and U_{osm} should rise, typically doubling. In a patient with NDI, UOP, U_{osm} and S_{osm} will not change. An example of a water deprivation test protocol is shown in Fig. 1.

Obtaining first-morning S_{osm}, U_{osm}, and serum sodium can also be used to suggest DI. In DI, the first morning S_{osm} will be hyperosmolar (>295 mOsm/kg), urine will be hypoosmolar (<300 mOsm/kg), and the serum sodium > 143 mEq/L. A concentrated U_{osm} (>600 mOsm/kg) indicates that DI is not present. It is important to not alter the patient's water intake when examining serum and urine sodium and osmolality except when the patient is under observation as described above.

If CDI is confirmed, an MRI of the brain and pituitary is recommended. Other pituitary hormone axes should also be screened given increased risk for developing anterior pituitary hormone deficits; growth hormone deficiency is the most common. Classic findings of CDI on MRI include a thickened

WATER DEPRIVATION TEST	
• Must be performed in a closely monitored inpatient setting • Place IV prior to start of test • STOP TEST at any point if patient exhibits sings or symptoms of hypovolemia	
Baseline (Time 0)	• Measure weight and vital signs • Obtain serum sodium, serum osm, serum BUN • Obtain urine sodium, urine osm, urine specific gravity by refractometer, and record urine output
Every hour	• Measure weight and vital signs • Obtain serum sodium, serum osm, serum BUN • Obtain urine sodium, urine osm, urine specific gravity by refractometer, and record urine output
During the Test: • If Serum Osm < 300 mOsm/kg, Na < 145, Urine Osm < 600 mOsm/kg, CONTINUE test unless vital signs suggest hypovolemia • If Urine Osm > 1000 mOsm/kg or > 600 mOsm/kg and stable for two voids, STOP test as patient does NOT have DI • If Serum Osm > 300 mOsm/kg and Urine Osm < 600 mOsm/kg, patient has DI. Give subcutaneous vasopressin 1 unit/m^2 subcutaneously and measure:	
At time of subcutaneous vasopressin	• Obtain vital signs • Obtain urine osm, urine specific gravity by refractometer, and record urine output
30 minutes and 60 minutes after subcutaneous vasopressin	• Obtain vital signs • Obtain urine osm, urine specific gravity by refractometer, and record urine output
• If patient has CDI, urine output will fall and urine osm will at least double in the hour after subcutaneous vasopressin administration • If patient has NDI, there will be no change in urine output or urine osm.	

Fig. 1. Water Deprivation Test Protocol *Adapted from Pediatric Endocrinology, 3rd Edition, Mark Sperling M.D. (Editor), "Disorders of the Posterior Pituitary," page 349., Copyright 2008, 2002, 1996, with permission from Elsevier.*

pituitary stalk or absence of the posterior pituitary bright spot. The presence of these findings is not a requisite for the diagnosis of DI. Lack of a posterior pituitary bright spot can be seen in CDI or in untreated NDI due to the body's release of stored vasopressin; it is not specific for CDI. The posterior bright spot is absent in 10% of normal newborn children, and the percentage increases by 1% per year of age [16]. In cases of acquired CDI where the MRI does not show a mass or lesion, current recommendations are to continue screening with MRI for a minimum of 3 years. Screening frequency can be determined by the clinical index of suspicion; often, follow-up MRI is done at 3 months and 6 months from CDI diagnosis. If no significant change is detected, MRI is repeated at 6 month intervals. In 61 patients with new onset DI without an established etiology, 7 were eventually diagnosed with a CNS germinoma, 4 with LCH, and 43 with idiopathic DI [13].

Initial management

Once the diagnosis of DI is confirmed, the mainstay of treatment for CDI is free access to water combined with a pharmacologic agent. Patients with mild DI may be treated only with increased fluid intake. However, in more severe DI, excessive fluid intake can lead to hydronephrosis, hydroureter and fluorosis; therefore treatment with a pharmacologic agent is recommended [12].

Synthetic vasopressin (Desmopressin/DDAVP) is used in older children (who do not depend primarily on fluids for their caloric needs). Various preparations as well as dose ranges and special considerations are listed in Table 2. Dosing is not weight- or age-based. At initiation, the lowest possible

Table 2
Medications used to treat DI.

A. Vasopressin Analogues used for central DI

Drug	Duration of action	Route	Dose	Special considerations	Notable side effects
Arginine vasopressin	5–10 min	IV	0.5–10 mU/kg/hr	- Requires close monitoring - Quick adjustments possible	- Hypertension - Intestinal cramping - Decreased intestinal blood flow
Vasopressin	2–8 h	IM or Subcutaneous	2.5–10 units, 2-4 times/day		
Desmopressin tablets	6–12 h	Oral	0.025–1.2 mg/day in 1–3 doses		
Desmopressin nasal spray (10mcg/spray)	5–21 h	Nasal	5–30 mcg/day in 1–2 doses	- Dose titration only in 10 mcg increments	- Rhinitis - Epistaxis - Nasal edema
Desmopressin aqueous solution	5–21 h	Nasal, via rhinal tube	10–40 mcg/day in 1–3 doses		- Rhinitis - Epistaxis - Nasal edema
Desmopressin lyophilisate (MinirinMelt)	6–20 h	Sublingual	1–4 mcg/kg/day in 2 doses	- Inaccurate splitting of tablets	

B. Other medications used to treat central and/or nephrogenic DI

Drug	CDI or NDI	Route	Dose	Notable side effects
Hydrochlorothiazide	CDI, NDI	PO	1–3 mg/kg/day in 1–2 doses	- Hypokalemia - Hyperuricemia - Hypercalcemia
Chlorothiazide	CDI, NDI	PO	5–10 mg/kg/dose 2–3 doses	- Hypokalemia - Hyperuricemia - Hypercalcemia
Indomethacin	NDI	PO	1–2 mg/kg day	- Bleeding - GI Upset
Amiloride	CDI, NDI	PO	0.3–0.625 mg/kg/day in 2 doses	- Hyperkalemia - GI Upset

dose of DDAVP is used, and individual response is assessed; both dose and frequency are determined based on individual response to medication. Patients should be allowed to void prior to repeat doses in order to excrete waste. Excretion of a typical solute load in a normal individual requires urine production of 6–10 ml/kg/day [17]. Under full antidiuretic effect of vasopressin, U_{osm} of 1000 mOsm/kg can be achieved, and excessive fluid intake can lead to hyponatremia [17]. The most common side effect of DDAVP is hyponatremia which can be avoided by allowing for adequate breakthrough UOP. Breakthrough can be defined as >4 ml/kg/hr of urine for 2 or more hours, specific gravity <1.005 and normal to increasing serum sodium. At home (where laboratory values are generally not measured) breakthrough is determined by having two large voids with clear, dilute urine.

DDAVP is available as an oral, intranasal, or subcutaneous preparation. Oral DDAVP is preferred over intranasal or subcutaneous DDAVP in older children and adolescents due to the ease of administration, easier dose titration, lower risk of hyponatremia and lack of necessity to refrigerate [1,18,19].

Management of infants and young children

While oral or intranasal DDAVP works well in children and adolescents with DI, management in infants, who are dependent on fluid such as breast milk or formula for nutrition, presents a challenge. Under 2 months of age, the minimum solute concentration of urine is 50 mOsm/L and the maximum is 700 mOsm/L, increasing to 1400 mOsm/L after 2 months of age. Therefore, even in infants without DI, many have an UOP greater than 5 ml/kg/hr (UOP ranges 400–12,000 ml/m^2/day versus 900 ml/m^2/day in children and adults) and will not concentrate greater than 150 mOsm/L due to the large amounts of fluid ingested to meet nutritional needs. Use of DDAVP leads to an increased risk of water intoxication and hyponatremia [16]. However, without treatment, these patients are at risk of dehydration and hypernatremia due to their inability to access adequate amounts of free water.

Thiazide diuretics are an appealing treatment alternative in this cohort. Thiazides decrease distal tubule reabsorption of sodium through inhibition of the Na–Cl cotransporter, inducing natriuresis and subsequent volume contraction. Volume contraction leads to increased water and sodium reabsorption in the proximal tubule, decreasing water delivery to the ascending loop of Henle where the filtrate is diluted [20]. Animal models have also shown that hydrochlorothiazide also acts on the inner medullary collecting ducts to increase water reabsorption by increasing insertion of aquaporin into the apical membrane; this antidiuretic effect is more pronounced with a low solute diet such as breast milk or low-solute formulas. Breast milk has a 20–30% lower solute load than does standard infant formula [21].

The recommended starting dose for thiazides is 1–3 mg/kg/day for hydrochlorothiazide or 10 mg/kg/day for chlorothiazide with dose adjustments based on UOP, sodium levels and side effects. No studies show that either is more efficacious. However, chlorothiazide is available in liquid form and is easier to administer to infants. In one study, no hyponatremia and one episode of post-operative hypernatremia secondary to limited access to free water was reported in infants with CDI treated with thiazides [22]. Other common side effects are hypokalemia and hypercalcemia. Hypokalemia can be managed with potassium supplementation or with the addition of amiloride starting at 0.3 mg/kg/day [23,24]. Amiloride blocks epithelial sodium channels in the distal convoluted tubule, inhibiting sodium resorption from the lumen and down-regulating the Na–K-ATPase leading to increased resorption of potassium. There are no adjunctive treatments for management of hypercalcemia, but it resolves with thiazide dose reduction. Previously, poor weight gain was reported with thiazide-based regimens but was not reproduced in subsequent studies [21,22]. Infants on thiazides show less variable sodium levels than do infants treated with DDAVP. With age, as the patient transitions to a primarily solid food based diet, the current recommendations are to transition to DDAVP. Thiazides are less efficacious with increased solute loads [16,22].

Desmopressin lyophilisate (Minirin Melt) is a newer treatment option for DI. Bioavailability of desmopressin lyophilisate is 60% greater than is bioavailability of DDAVP tablets with similar levels of efficacy. Desmopressin lyophilisate allows administration of smaller doses, and studies show more stable absorption than DDAVP intranasal spray or oral tablets. In case reports, starting doses of

1–2 mcg/kg/day were used in 6 infants; they displayed appropriate weight gain and had no hypernatremia or hyponatremia during the first two years of life [25,26].

Subcutaneous DDAVP administration allows for the use of small doses in infants but shows more variable sodium levels than do other formulations. The recommended starting dose is 0.01 mcg daily with titration based on patient response [16]. Injectable DDAVP can be diluted 1:10 with sterile water if a smaller dose is needed. In comparison to intranasal DDAVP, injectable DDAVP has shown no episodes of severe hyponatremia. Patients did have mild hyponatremia, and control was not better than with use of intranasal DDAVP [27].

Management in the adipsic patient

Normally, vasopressin is secreted at a S_{osm} of 285 mOsm/kg, and thirst is triggered at a S_{osm} of 290 mOsm/kg. However, some individuals with DI fail to have appropriate thirst when S_{osm} rises, leading to life-threatening hypernatremia or hyponatremia with inappropriate fluid consumption at lower serum osmolalities [16]. In contrast, one third of patients who develop DI following craniopharyngioma resection are adipsic with disruption of both osmotic and non-osmotic pathways, demonstrated by a lack of thirst after administration of a hypertonic saline infusion or a fall in blood pressure [28]. Management has been successful using a fixed daily fluid regimen with DDAVP administered at doses allowing for appropriate UOP. Fluid amounts require regular adjustment with weight gain. Patients are weighed when eunatremic and a fluid regimen is determined based on maintenance requirements and estimated insensible losses. Fluid intake is adjusted based on daily weights, adding or subtracting 1 liter per 1 kg change in weight [29]. For example, if an ideal weight is 60 kg with daily fluid intake of 1.5 L and the patient now weighs 61 kg, the fluid intake would decrease by 1 L. During times of illness, fluid requirements may acutely vary, necessitating closer monitoring and more frequent sodium checks to maintain hydration and normonatremia [30].

Monitoring and management of DI post-operatively

After intracranial surgery, patients are at risk for DI. Historically, 80% of patients with craniopharyngiomas have DI post-operatively; 13% are transient. More patients are likely to have transient versus permanent DI when using a transsphenoidal instead of a transfrontal surgical approach [28]. Frequently, patients have a triphasic response with initial DI at 24–48 h post-operatively, syndrome of inappropriate antidiuretic hormone (SIADH) between 2 and 10 days and either resolution or transient or permanent DI in days to weeks post-operatively [31].

Prior to pituitary surgery, it is prudent to obtain S_{osm} and U_{osm} to rule out DI as this alters preoperative and surgical fluid management. All patients having surgery in the area of the pituitary need close monitoring of fluid intake, UOP and serum sodium levels. If UOP exceeds 4 ml/kg/hr, S_{osm} and U_{osm} should be measured. If urine is non-concentrated (<600 mOsm/kg) in the setting of a $S_{osm} > 300$, DI is diagnosed. However, UOP can be greater than 4 ml/kg/hr with dilute urine in the setting of normal S_{osm} secondary to post-operative fluid shifts in the first 24–48 h after surgery.

There are no evidence-based studies that determine optimal fluid management in children with DI requiring intravenous fluids. The only consensus is that hypotonic fluids should be administered [12,17,32]. A recent study showed increased risk of negative outcomes using normal saline (NS) in these patients and the best outcomes using 0.45NS compared to D_5 water [32]. Some investigators recommend using 40 ml/m^2/hr D_5 + 0.2NS as a basal rate and replacing UOP greater than 40 ml/m^2/hr with D_5 Water [17]. Another common method is replacing UOP ml per ml with 0.45NS and not accounting for insensible losses [28]. At our institution, insensible fluid replacement is initiated with D_5 + 0.45NS with 20 mEq/L KCl at 300–500 ml/m^2/day in addition to UOP replacement with 1 ml of $D_{2.5}$ + 0.2NS for every 1 ml of UOP. Fluid rates are adjusted based on sodium trends and ongoing losses. No significant hyponatremia or hypernatremia has occurred at our institution using this regimen.

Treatment with low-dose DDAVP is considered in cases where it is difficult to replace ongoing losses. Treatment regimens include 0.05 mg oral DDAVP, 5–10 mcg intranasal DDAVP, 0.1–0.2 mcg subcutaneous DDAVP or a continuous vasopressin infusion at 1–3 mU/kg/hr. Vasopressin infusions are typically used in an intensive care setting. Following a medication dose, the patient is closely monitored for breakthrough UOP as described above prior to receiving further DDAVP [28]. If the patient does not breakthrough or UOP decreases, they are monitored on the same fluid regimen and evaluated for resolution of DI, delayed breakthrough, or evolution to SIADH. It is safe to use low dose DDAVP even in those patients with subsequent development of SIADH with close monitoring of UOP, sodium levels and careful control of fluid intake.

Patients undergoing pituitary surgery are also at risk of post-operative ACTH deficiency. Untreated ACTH deficiency can mask existing DI due to the overproduction of corticotrophin releasing hormone (CRH). CRH and vasopressin are both produced by the parvocellular neurons. In adrenal insufficiency, CRH production is increased with a concomitant increase in vasopressin production, leading to antidiuresis. Cortisol deficiency also causes decreased free water clearance through stimulation of a nitric-oxide mediated pathway resulting in insertion of aquaporin channels in the renal collecting duct independent of vasopressin stimulation and increased free water absorption [12]. Once glucocorticoid therapy is initiated, negative feedback decreases CRH and associated vasopressin secretion from the parvocellular neurons in conjunction with down regulation of the nitric-oxide pathway resulting in polyuria and “unmasking” of DI.

Nephrogenic DI

Approximately 90% of cases of congenital NDI occur secondary to XLNDI with mutations in the vasopressin receptor, and 10% are secondary to autosomal dominant or recessive mutations of AQP2. Initial treatment of NDI with thiazide diuretics and a low solute diet (9 mEq NaCl/day) decreases UOP by as much as 70% [33]. Further UOP reduction can be achieved with protein restriction; this often results in poor growth and poor compliance. Side effects of thiazide diuretics are reviewed above, with hypokalemia being the most common. Hypokalemia can be treated with the use of potassium supplementation or addition of amiloride. Amiloride and hydrochlorothiazide together can not only improve hypokalemia but also achieve similar UOP reduction as a thiazide in conjunction with indomethacin [34]. Indomethacin, a nonselective cyclo-oxygenase inhibitor, antagonizes prostaglandin synthesis leading to enhanced proximal tubule water reabsorption and reducing UOP 25–50% further than thiazides alone [33]. Common side effects of indomethacin, such as abdominal pain or gastric bleeding can be reduced if taken with meals or with the addition of a proton pump inhibitor. Unfortunately, current management strategies for NDI are sub-optimal at best; patients still experience significant polyuria and polydipsia and require monitoring for the development of hydroureter.

Multiple investigational drugs are being examined to improve NDI treatment. Class II V2R mutations are the most common mutations producing NDI, causing abnormal folding of the V2R (Chapter 8). The V2R is retained in the endoplasmic reticulum and is unable to migrate to the apical membrane of the collecting duct to facilitate reabsorption of water. V2R nonpeptide agonists have shown greater efficacy than have antagonist chaperones in specific mutations by facilitating proper folding of V2R and insertion into the plasma membrane resulting in functionality of the channel. AQP2 water channel chaperones are under investigation as well [33–35]. Unfortunately, the first clinical trial on V2R antagonists was terminated secondary to hepatotoxicity from effective doses [20].

Further studies are needed to investigate multiple mechanisms that can bypass the V2R, which would be of use in both V2R and AQP2 mutations. As AQP2 rapidly cycles between the apical membrane and intracellular membrane, the rationale behind many interventions is both to promote exocytosis and to prevent endocytosis of AQP2 replacing the need for vasopressin which usually stabilizes AQP2 within the apical membrane via a G-protein coupled receptor pathway. Therefore, research has focused on activation of cAMP or downstream effectors in that pathway. Statins inhibit 3-hydroxy-3-methylglutaryl-coenzyme A thereby decreasing LDL and cholesterol; this also decreases mevalonate, which in turn decreases the action of Rho-GTPase leading to

depolymerization of actin and promoting AQP2 expression on the cell surface and decreasing rates of endocytosis [33,35,36]. While statins have effectively decreased UOP *in vivo* in mouse models, fluvastatin did not decrease UOP in an individual with XLNDI on a therapeutic dose of statins for hypercholesterolemia [35]. Further research is needed regarding the dose effect of different statins, duration of treatment and safety for the use in children. Phosphodiesterase 5 inhibitors have been shown to activate the cGMP pathway and promote insertion of AQP2 *in vivo* and *in vitro* in the apical membrane of the outer medullary collecting duct but do not change insertion in the cortical collecting duct which is the major site of water reabsorption [23]. However, there is one case report of sildenafil treatment in a 4 year old male with XLNDI whose UOP dropped from 1764 ml/day on hydrochlorothiazide, amiloride and indomethacin to 950 ml/day using sildenafil [37].

Management of DI during chemotherapy

Management of DI is more complex in patients requiring excessive fluid for chemotherapy infusions or surgery. In these settings, the recommendation is to hold DDAVP doses as the patient's usual dose in conjunction with high fluid volume could result in severe hyponatremia. Even with UOP replacement in excess of chemotherapy fluids received, patients can experience significant polyuria and hypernatremia. Low-dose continuous vasopressin infusion has been effective at decreasing UOP and at maintaining normal sodium levels. Vasopressin drips are started conservatively at 0.08 mU/kg/hr with dose titration to keep the urine specific gravity between 1.004 and 1.009 while maintaining weight, UOP and electrolyte balance. Close monitoring of fluid intake and output, weight, urine specific gravity and serum sodium levels is required. Treated patients can maintain a relatively normal UOP, closer to 3.8 L/m^2/day as opposed to untreated patients who require 20 L/m^2/day to maintain hydration and normal electrolyte levels [38].

Medication-induced DI

DI can be a side effect of many medications, including psychotropic medications, chemotherapeutic agents, and antimicrobials. Common offending agents are listed in Table 1.

Lithium is the most common culprit, accounting for 12–40% of all medication-induced DI. DI occurs in 20% of individuals on lithium therapy [39]. Lithium causes NDI by acutely leading to epithelial sodium channel (ENaC) mediated influx of lithium into principal cells, downregulation of AQP2 and diminished free water absorption. Chronically, lithium induced nephrotoxicity leads to loss of principal cells [40,41]. Increased prostaglandin (PGE2) levels also contribute to polyuria. Lithium does not affect the procoagulant effects of vasopressin, suggesting it selectively impairs vasopressin action in the kidneys.

Summary

Diagnosing and establishing the etiology of DI can be difficult. Once confirmed, management of polyuria and polydipsia poses its own challenges. After the diagnosis of CDI is made, MRI of the pituitary, screening of all anterior pituitary hormones for associated hormonal deficits and appropriate further work up based on results should be performed. The mainstay of treatment in children with CDI remains administration of DDAVP to maintain sodium homeostasis and improve quality of life. In infants with DI, the literature supports use of thiazide diuretics as a safer alternative to DDAVP because they are dependent on liquid for nutrition and lack free access to fluids. Management of DI in patients requiring intravenous fluids needs further attention as no evidence based studies exist to determine optimal fluid choice and fluid rates. NDI is currently managed with thiazide diuretics; however additional research is necessary to optimize management and promising alternatives are on the horizon.

Practice points

- Suspect DI in a patient with polyuria, polydipsia, new enuresis, growth failure, suprasellar mass, or associated congenital defects or syndromes.
- *Establish diagnosis*
  - 24 h urine collection
  - Random serum osmolality >300 mOsm/kg with urine osmolality <600 mOsm/kg
  - Water deprivation test
  - Assess response to vasopressin to differentiate between CDI and NDI
- *General Management Considerations*
  - Never limit fluid intake unless the child is in a closely monitored medical setting or fluid needs have already been established as in the case of an adipsic patient
  - If thirst intact, the child will require free access to water and the addition of a vasopressin analogue if polyuria and polydipsia is profound and/or causing disruption to their quality of life.
- *CDI Management in Special Populations*
  - Infants with CDI
    - Thiazide diuretics are preferred to DDAVP to allow for adequate nutrition
    - Transition from a thiazide to a vasopressin analogue is considered when a child primarily ingests solid foods for nutrition.
  - Children and Adolescents with CDI
    - Oral DDAVP is efficacious, safe and has greater adherence than other formulations
    - Dose and dosing frequency are determined on an individual basis depending on dose response.
    - Always allow for urine breakthrough prior to re-dosing
  - Patients with CDI and Adipsia
    - Treatment goal is normonatremia and adequate hydration on a set vasopressin dose and fluid regimen allowing for breakthrough urination
    - Close monitoring of weight, intake, and output is necessary.
    - Fluid prescription can be modified based on daily weight, accounting for normal growth.
  - Post-operative Neurosurgical Patients
    - Monitor intake, urine output, serum sodium, and urine specific gravity closely.
    - Fluid management should be titrated based on serum sodium levels as well as urine and serum osmolarity.
  - DI During Chemotherapy Administration
    - Hold patient's DDAVP
    - In patients with CDI receiving large amounts of fluid (>3 $L/m^2/d$), low dose (0.08 mU/kg/hr) IV vasopressin should be considered to limit UOP and risk of hypernatremia. Titrate vasopressin based on UOP and sodium levels.
- *NDI Management*
  - Free access to water and a low solute diet
  - Currently approved pharmacologic agents include thiazide diuretics with the addition of amiloride or indomethacin.
- *Research Points*
  - Further understanding of acquired CDI etiologies is needed – 40% of patients currently have no identifiable cause.
  - Management in Infants
    - Further studies comparing the efficacy of hydrochlorothiazide vs chlorothiazide
    - Comparing the efficacy of amiloride + thiazide diuretic with indomethacin + thiazide
    - Dosing, safety, and efficacy studies of sublingual desmopressin lyophilisate (MinirinMelt)
  - Nephrogenic DI
    - AVPR2 chaperones, specifically nonpeptide agonists and antagonists
    - AQP2 chaperones
    - Medications that bypass AVPR2 such as statins, phosphodiesterase inhibitors, sodium nitroprusside, calcitonin, prostaglandins, and heat shock protein 90 inhibitor

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