Vasopressin-Dependent Disorders: What Is New in Children?

Jane E. Driano,[a] Aida N. Lteif, MD,[b] Ana L. Creo, MD[b]

abstract

Arginine vasopressin (AVP)–mediated osmoregulatory disorders, such as diabetes insipidus (DI) and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) are common in the differential diagnosis for children with hypo- and hypernatremia and require timely recognition and treatment. DI is caused by a failure to concentrate urine secondary to impaired production of or response to AVP, resulting in hypernatremia. Newer methods of diagnosing DI include measuring copeptin levels; copeptin is AVP's chaperone protein and serves as a surrogate biomarker of AVP secretion. Intraoperative copeptin levels may also help predict the risk for developing DI after neurosurgical procedures. Copeptin levels hold diagnostic promise in other pediatric conditions, too. Recently, expanded genotype and phenotype correlations in inherited DI disorders have been described and may better predict the clinical course in affected children and infants. Similarly, newer formulations of synthetic AVP may improve pediatric DI treatment. In contrast to DI, SIADH, characterized by inappropriate AVP secretion, commonly leads to severe hyponatremia. Contemporary methods aid clinicians in distinguishing SIADH from other hyponatremic conditions, particularly cerebral salt wasting. Further research on the efficacy of therapies for pediatric SIADH is needed, although some adult treatments hold promise for pediatrics. Lastly, expansion of home point-of-care sodium testing may transform management of SIADH and DI in children. In this article, we review recent developments in the understanding of pathophysiology, diagnostic workup, and treatment of better outcomes and quality of life for children with these challenging disorders.

Pediatric providers commonly encounter children with hypo- or hypernatremia.[1] Arginine vasopressin (AVP)–dependent conditions, such as diabetes insipidus (DI) and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) are frequent in the differential diagnosis for children presenting with sodium or fluid abnormalities. Diagnosing DI and SIADH remains challenging, and prompt management is needed to prevent morbidity. Considerable advances in the understanding of pathophysiology, diagnostic processes, and treatment of children with these disorders have been made. Our aim is to review how to approach these disorders in children and highlight recent scientific developments.

PHYSIOLOGY OF OSMOREGULATION: PRODUCTION AND ACTION

AVP is derived from a preprohormone produced by magnocellular neurons within the paraventricular and supraoptic hypothalamic nuclei,[2–4] along with its carrier protein, neurophysin II, and chaperone protein, copeptin.[5] The magnocellular neurons terminate in the posterior pituitary

[a]School of Medicine, Creighton University, Omaha, Nebraska; and [b]Division of Pediatric Endocrinology and Metabolism, Mayo Clinic, Rochester, Minnesota

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Address correspondence to Ana L. Creo, MD, Division of Pediatric Endocrinology and Metabolism, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail: creo.ana@mayo.edu

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stalk[4] in which enough AVP is stored for a sustained antidiuretic effect of 5 to 10 days.[6] AVP initiates its antidiuretic effect on renal epithelial cells of the collecting duct via the vasopressin-2 receptor (V2 receptor).[2,3,7] Renal aquaporin channels facilitate water movement from the lumen into systemic circulation.[3,7–11] AVP curtails water excretion and promotes renal water reabsorption.

Increasing serum osmolality, hypovolemia, and arterial hypotension stimulate AVP release. The organum vasculosum and the subfornical organ serve as central osmoreceptors, sensing disruptions in plasma osmolality through changes in cell volume.[2,4,12,13] At a serum osmolality threshold of ~280 mOsm/kg, AVP is released relative to the increasing osmolality.[3,14] Osmolality is the most potent AVP stimulus, with a 1% change in serum osmolality stimulating AVP release.[2,7,12,14] Children release more AVP compared with adults with the same osmolality.[7,15] The sensation of thirst is governed by the ventromedial hypothalamic nucleus and triggered by increasing serum osmolality.[14] AVP is also secreted in response to a 5% to 10% decrease in systemic pressure, as monitored by carotid sinus baroreceptors.[2,3,7,14,16] Similarly, hypovolemia sensed by left atrium baroreceptors triggers AVP release.[2,3,14,16] Lastly, nausea and emesis also induce AVP secretion via the emetic reflex itself by overriding the setpoint for AVP secretion and therefore inducing AVP release.[2,3,14,17]

DI

Epidemiology

DI, defined by failure to concentrate urine secondary to serum osmolality increases, has a prevalence of 1 in 25 000 people.[5] DI presents at variable ages on the basis of etiology.[18] Of children with DI, 90% have central DI, whereas 10% have nephrogenic DI.[5] Approximately 10% of all DI cases are heritable, with 90% being X-linked nephrogenic DI and 10% from autosomal dominant and recessive cases.

Pathophysiology

Central DI causes an inability to concentrate urine secondary to a loss of AVP production or secretion.[8] It occurs after a loss of >80% of the sellar magnocellular neurons.[5] In familial cases of central DI with accumulation of mutated neurophysin II, sellar anatomic abnormalities can be seen on autopsy with gliosis in the paraventricular and supraoptic hypothalamic nuclei.[19,20] nephrogenic DI results from reduced or absent response to AVP with normal production and release.[8]

Etiology

Inherited Forms of Central DI

More than 70 different mutations in the *AVP NPII* gene have been implicated in central DI, (Table 1)[21] occurring in the AVP, NPII, and signal sequences, but none have been identified in the copeptin moiety.[22] Although the exact mechanism of a specific mutation's effect remains unknown, accumulation of mutated AVP precursor in the endoplasmic reticulum likely impairs AVP processing and secretion.[23] Autosomal dominant central DI is more common than autosomal recessive DI and typically presents after age 1, whereas autosomal recessive forms present 1 to 2 weeks after birth.[10] However, wide variation in the age at presentation, even between children with the same genetic markers, suggests different rates of synthesis or clearance.[5] Another genetic marker is a mutation in the *PCSK1* gene, the product of which processes AVP.[24]

Type 1 Wolfram syndrome, an autosomal recessive condition caused by loss-of-function mutation in the *WFS1* gene or missense mutation in the *ZCD2* gene,[25,26] is characterized by central DI due to abnormal AVP processing or neuronal migration,[25] diabetes mellitus, and optic degeneration.[22]

Septo-optic dysplasia, in both its spontaneous and inherited forms, can result in central DI[8,27] secondary to dysfunction of the central osmoreceptors.[28] In children with central DI, the prevalence of septo-optic dysplasia is 15%.[29]

Acquired Forms of Central DI

At least 50% of acquired central DI forms are initially diagnosed as idiopathic.[30] However, Werny et al[29] suggest an alternate diagnosis is identified in almost 20% of these children and within 3 years of that diagnosis. One such diagnosis is autoimmune-mediated DI. Maghnie et al[31] identified AVP-secreting cell antibodies AVPc-Abs in 75% of children with idiopathic central DI. However, these nonspecific antibodies have also been found in affected patients with other definitive causes of DI, such as Langerhans cell histiocytosis, germinomas, and postoperative DI.[31,32] The autoimmune mechanism is strengthened by a temporal relationship between viral infection and onset of central DI in ~25% of idiopathic cases.[30] Additional autoimmune conditions associated with central DI secondary to hypophysitis include rabphilin-3A autoantibodies and IgG4-related systemic syndrome.[33,34]

Langerhans cell histiocytosis is identified in 12% of children with acquired central DI.[29] Typically, other symptoms of Langerhans cell histiocytosis precede those of central DI by 1 year.[35] Central DI is its most common central nervous system (CNS) manifestation,[36] occurring in 17% to 25% of children with the disease,[35] most likely because of hypothalamic infiltration and subsequent scarring.

TABLE 1 Comparison of DI Versus SIADH

	Central DI	Nephrogenic DI	SIADH
Common etiology in children			
Inherited	*AVP NPII* gene mutation[21]	X-linked V2 receptor mutation[5]	V2 receptor mutation[22]
	PCSK1 gene mutation[24]	Autosomal dominant and recessive aquaporin-2 channel mutations[5,8]	*GNAS* gene mutation[98]
	WFS1 or *ZCD2* gene mutation[25,26]		*TRPV4* gene mutation[125]
	Congenital hypopituitarism[126]		
Acquired	Idiopathic[8,29]	Drugs: lithium, demeclocycline, foscarnet, clozapine, amphotericin B, methicillin, rifampin[68]	Idiopathic[12]
	Brain malformations[8,29]: septo-optic dysplasia, holoprosencephaly	Hypercalcemia[7]	Cytotoxic agents[85]: cyclophosphamide, vincristine
	Infiltrative[8,29]: Langerhans cell histiocytosis, sarcoidosis, tuberculosis	Hypokalemia[7]	Anticonvulsants[85,94]: carbamazepine, oxcarbazepine
	Brain tumor[8,29]: craniopharyngioma, germinoma	Apparent mineralocorticoid excess[40]	Antidepressants[85,95]: SSRIs, tricyclic
	Infection[7,8]: meningitis, encephalitis	Chronic renal disease: cystinosis, nephronophthisis, Bartter syndrome[7,40]	Pain medication[85,104]: NSAIDs, narcotics
	Trauma[7,8,29]: traumatic brain injury, hypoxic insult, surgery	Osmotic diuresis: diabetes mellitus[7]	dDAVP[104]
	Supraventricular tachycardia[127]	Sickle cell disease[128]	Infection[12,85,104]: febrile disease, pneumonia
	Anorexia nervosa[129]	Ureter obstruction[130]	Pulmonary disease[12,85]: asthma, cystic fibrosis, bronchiolitis
		Bardet-Biedl disease[131]	Malignancies[85]: lymphoma, carcinoma, Ewing sarcoma, cerebral tumors
			Trauma[12,104]: traumatic brain injury, surgery
			HIV or AIDs[12]
Signs and symptoms	Hypernatremia	Hypernatremia	Hyponatremia
	Polyuria[7]: >150 mL/kg per d in neonates, >100–110 mL/kg per d in children aged up to 2 y, >40–50 mL/kg per d in older children	Polyuria rarely exceeds 3–4 L/d[43]	Oliguria[101]
	Polydipsia	Polydipsia	Euvolemia[12]
	Symptoms in infants[68]: fever, vomiting, failure to gain weight	Symptoms in all ages[68]: recurrent fevers, vomiting, growth failure, mental retardation	Symptoms[85,104]: headache, nausea, vomiting, muscle cramps, lethargy, restlessness, confusion, seizures
	Symptoms in older children[68]: disturbed sleep, lethargy, nocturia		
	Symptoms in all ages[68]: irritability, dehydration, potential seizures		
Differential	Diabetes mellitus[8]	Diabetes mellitus[8]	Hyponatremia hypovolemia[85,95]: cerebral

Brain tumors are another common cause of acquired central DI. Werny et al[29] noted 35% of children presenting with central DI were ultimately found to have brain tumors. Central DI can present because of tumor invasion or postoperatively after debulking surgeries.[5,37,38] Craniopharyngiomas and germinomas are the most common brain tumors that invade the sella and cause DI.[5,39] Because these tumors are slow growing, DI may manifest before identification of the tumor on imaging, with a median 1 year lag in time between presentation of DI to germinoma diagnosis.[30] Thus, MRIs are recommended every 3 to 6 months postdiagnosis of acquired idiopathic DI for at least 2 years if, on initial MRI, there is a widened pituitary stalk.[5]

Forms of Nephrogenic DI

Medications and electrolyte abnormalities commonly cause nephrogenic DI (Table 1).[7,8] Renal disease and obstruction can also be implicated.[40] The most common form of inherited nephrogenic DI is X-linked, caused by a V2 receptor mutation.[5] Less commonly, there are autosomal dominant and recessive mutations in the aquaporin-2 channel known to cause nephrogenic DI.[5,8]

Clinical Signs and Symptoms

Similar to central DI, children with nephrogenic DI present with polydipsia and polyuria.[41] They often prefer cold water over other beverages.[39] Unusual water-seeking behaviors may occur from puddles, vases,[39] or toilets.[7] Infants or children with developmental delay may experience unintentional fluid restriction, leaving them especially vulnerable to hypernatremia.[42] Children with DI may have primary or secondary nocturnal enuresis.[8,39] Children with nephrogenic DI typically have less severe polyuria and polydipsia compared with those

TABLE 1 Continued

	Central DI	Nephrogenic DI	SIADH
			salt wasting, GI loss, severe burns, acute sequestration into third spaces
	Nephrogenic DI[8] Renal disease[8] Hypercalcemia[8] Iatrogenic[16] Dehydration[16] Primary polydipsia[7]	Central DI[8] Renal disease[8] Hypercalcemia[8] Iatrogenic[16] Dehydration[16] Primary polydipsia[7]	Hyponatremia hypervolemia[12,85,95]: congestive heart failure, cirrhosis, nephrotic syndrome, iatrogenic
Diagnostic criteria	Serum glucose, calcium, potassium, SUN levels within normal limits[8]	Serum glucose, potassium, SUN levels within normal limits[8]: hypercalcemia is a potential etiology	Essential criteria[103]: effective serum osmolality <275 mOsm/kg; urine osmolality >100 mOsm/kg; clinical euvolemia; urine sodium concentration > 30 mmol/L; absence of adrenal, thyroid, pituitary, or renal insufficiency; no recent diuretic agents
	Current protocol: water deprivation testing[8]: serum osmolality >300 mOsm/kg with simultaneous urine osmolality <300 mOsm/kg, dDAVP increases urine osmolality >750 mOsm/kg Future potential protocols: hypertonic saline-induced serum copeptin[50]; Water deprivation test coupled with serum copeptin measurements[56]: <2.2 pmol/L (central DI), 2.2–5 pmol/L (central DI or primary polydipsia), >5–20 pmol/L (primary polydipsia), >20 pmol/L (nephrogenic DI)	Current protocol: water deprivation testing[8]: serum osmolality >300 mOsm/kg with simultaneous urine osmolality <300 mOsm/kg, dDAVP administration fails to increase urine osmolality Future potential protocol: elevated baseline copeptin measurement >20 pmol/L[48]	Supplemental criteria[103]: serum uric acid level <0.24 mmol/L, serum urea level <3.6 mmol/L, failure to correct hyponatremia after 0.9% saline infusion, fractional sodium excretion >0.5%, fractional urea excretion >55%, fractional uric acid excretion >12%, correction of hyponatremia through fluid restriction

GI, gastrointestinal; SSRI, selective serotonin reuptake inhibitors.

with central DI.[43] Not all children with central DI have polydipsia because some lack thirst (adipsia) because of midline CNS abnormalities[44] or autoantibodies against[45] central osmoreceptors.[42,46] Many cases of central DI are due to intracranial tumors, so symptoms, such as headaches, vomiting, growth retardation, and fatigue should be assessed.[8,30] However, growth retardation and poor weight gain may stem from a preference for water over food[8] and not be associated with an intracranial tumor.[5]

Diagnostic Criteria

In hospitalized children, the incidence of hypernatremia, at a serum sodium level >150 mEq/L, has been estimated at 1.4%.[47] Hypernatremia can be attributed to excessive fluid loss, such as gastroenteritis or solute diuresis, decreased fluid intake, or inappropriate salt intake.[47] Inappropriate salt intake rarely results from poisoning but can inadvertently occur with administration of 0.9% saline in children with DI because the concentration of salt overwhelms the child's ability to excrete it, given that urine osmolality is typically low. A laboratory workup may help rule out these other causes. Serum glucose, calcium, potassium, and serum urea nitrogen (SUN) levels within normal limits should raise clinical suspicion of DI.[8] Serum osmolality levels >300 mOsm/kg and urine osmolality levels <300 mOsm/kg suggest DI.[8] Primary polydipsia also presents with polydipsia and polyuria, although it may cause slight hyponatremia.[7] It is characterized by inappropriate fluid intake,[48,49] which downregulates AVP secretion[43] and aquaporin-2 channels.[49] The water deprivation test is the current gold standard to establish the child's ability to concentrate urine.[8] During testing, the child abstains from all oral and IV fluids with hourly serum sodium and osmolality, urine osmolality, specific gravity, and urine volume measurements.[8] At many institutions, a urine osmolality level >1000 or >600 mOsm/kg and stable for 2 voids rule out DI; the patient may instead have primary polydipsia.[8,49] If the serum osmolality level is >300 mOsm/kg and the urine osmolality level is <300 mOsm/kg, the child is diagnosed with DI.[5] However, diagnostic accuracy of the water deprivation test is only ~70%,[49] perhaps because of difficulty in diagnosing partial DI and downregulation of AVP production in patients with polydipsia.[43,49,50] To differentiate central from nephrogenic DI, administration of deamino-8-D-arginine vasopressin (dDAVP) will increase urine osmolality of >750 mOsm/kg only in central DI.[8]

Tumor markers α-fetoprotein and human chorionic gonadotrophin used to screen for neoplasms[7] and an MRI of the pituitary gland are

recommended when a child is diagnosed with central DI.[5,29] Although not specific to central DI, the degree of a posterior pituitary hypointensity correlates with duration of transient central DI.[8,51,52] A thickened pituitary stalk, seen in 33% of pediatric patients with DI, is associated with Langerhans cell histiocytosis, germinomas, and hypophysitis.[5,53]

Copeptin, a Novel Biomarker

The copeptin assay has become more widely available in clinical chemistry laboratories and is gaining popularity because of the stability of this peptide in plasma.[54] When it was compared with serum AVP, Balanescu et al[55] found copeptin more closely correlated with plasma osmolarity, rendering it a better diagnostic marker for vasopressin-mediated disorders. Pediatric copeptin reference ranges have not been formally established; however, levels in healthy, non–water-deprived children likely range from 2.4 to 9.0 pmol/L.[56,57] Copeptin values vary slightly between sexes in adults[58] and neonates.[59] They do not vary with age in adults and are thought to be similar to adult basal levels within a day of birth if the neonate is healthy.[58,60]

The role of copeptin in diagnosing osmoregulatory disorders has been studied more in adults than children. Fenske et al[48,50] found the change in ratio of copeptin to serum sodium concentrations over time improved the diagnostic accuracy of the water deprivation test, which was challenged in a later study. Stimulated plasma copeptin levels by using a hypertonic saline infusion were used to more accurately diagnose DI than the water deprivation test, with a diagnostic accuracy of 96.5%[50] and may replace the water deprivation test at some institutions.[61]

Copeptin is currently used in pediatrics to quantify neonatal stress, such as asphyxia and hypothermia.[62–65] Other studies have analyzed the role of copeptin as a prognostic biomarker in pediatric conditions, as reviewed in Table 2. However, in the acute setting, a cautious interpretation of serum copeptin should be made because of potential multifactorial influences on AVP secretion.[66] There have been limited studies on the role of copeptin in pediatric osmoregulatory disorders. Tuli et al[56] analyzed water deprivation-induced copeptin in the differential of polyuria-polydipsia syndrome, proposing cutoffs of copeptin values for diagnosis of central DI, partial central DI, primary polydipsia, and nephrogenic DI in children. An elevated baseline copeptin value could be used to diagnose nephrogenic DI without a water deprivation test or hypertonic saline bolus,[48,56] as was done in an infant presenting with polyuria-polydipsia and poor weight gain.[67] Copeptin levels normalized after successful treatment in the infant, suggesting copeptin levels could indicate responsiveness to treatment of polyuria-polydipsia syndromes.

Treatment

For DI, first-line treatment is unrestricted water access and a low sodium diet, which may be particularly effective for children with nephrogenic DI (Table 3).[8,68] Adjustments may be necessary to achieve proper hydration and nutritional status. Intermittent catheterization or cystostomy should be introduced for postvoiding residual volume.[69] However, some children with central DI may require synthetic vasopressin (desmopressin or dDAVP) if their polyuria persists. dDAVP has a longer duration of action[8,44] than endogenous AVP, with a half-life of 3.5 hours.[5] Oral or intranasal formulations are preferred in older pediatric patients because of better compliance and absorption.[5,70]

TABLE 2 Potential Pediatric Applications of Copeptin as a Biomarker

Classification	Proposed Mechanism	Conditions
Osmoregulatory disorders	Fluctuations in serum osmolality induce AVP secretion.	DI (central and nephrogenic)[56,67] Polyuria-polydipsia syndrome[56,67] Nocturnal enuresis[132,133] Acute postsurgical AVP disruptions
Critical illness	In adults, acute phase cytokines can elevate copeptin levels.[134]	Pneumonia and complications[57,135,136] Traumatic brain injury and prognosis[137] Post–cardiac surgery complications[138] Children with high mortality risk[139]
Perinatal illness	States of physical stress such as decreased serum pH and asphyxia secondary to delivery or other etiologies likely induce AVP and copeptin secretion.[140]	Vaginal delivery versus cesarean delivery[140–142] Asphyxia[64,140] Mechanical ventilation[63] Hypoxic-ischemic encephalopathy[143] Maternal preeclampsia[144,145] Fetal acidosis[140,146]
Other pediatric conditions	—	Type 1 diabetes and complications[147,148] Obesity[149] Cystic fibrosis[150] Primary hypertension[151] Efficacy of treatment in postural orthostatic tachycardia syndrome[152,153] Febrile seizure[154,155] Maltreatment[156] Psychological stress[157]

—, not applicable.

TABLE 3 Review of Pharmacologic Therapy for Central DI

Therapy	Average Dose	Mechanism of Action
dDAVP: oral, intranasal, subcutaneous[7,8]	Oral: 50–200 μg/d (2–3 doses; child), 100–500 μg/d (2–3 doses; adolescent) Intranasal: 2.5–10 μg/d (2–3 doses; child), 10–20 μg/d (2–3 doses; adolescent) Subcutaneous:0.01 μg/d (1 dose; infant), 0.3–0.5 μg/d (1 dose; child), 0.5–1 μg/d (1 dose; adolescent)	Synthetic vasopressin activates V2 receptor
Thiazide diuretics[8]	Hydrochlorothiazide: 1–3 mg/kg per d (in up to 2 doses) Chlorothiazide: 5–10 mg/kg/d (in 2–3 doses)	Inhibit sodium chloride cotransporter to reduce reabsorption of sodium in distal tubule; consequently, it enacts sodium and water reabsorption in the proximal tubule, so less water dilutes the filtrate in the ascending loop of Henle
Desmopressin lyophilizate[8]	1–2 μg/kg per d	Synthetic vasopressin activates V2 receptor
Amiloride[8]	0.3–0.625 mg/kg per d	Potassium-sparing diuretic
Chlorpropamide[7,a,b]	<150–350 mg/d	Potentiates secretion of AVP, increase reactivity of V2 receptor to basal levels of endogenous AVP
Carbamazepine[7,a,b]	200 mg/d (up to 2 doses per d)	Increases reactivity of V2 receptor to basal levels of endogenous AVP

[a] Not recommended for use in children because of adverse side effects.
[b] Pediatric dosing not fully established.

The major risks of dDAVP are hyponatremia and potential extrapontine myelinolysis in the presence of multidrug therapy if hypernatremia is rapidly reversed.[71] Thus, the first dose should be small and then increased to find the child's therapeutic window.[7] Dosing is based on symptom control, not age or weight.[8,44]

Treating infants with central DI poses additional challenges. Because they rely on fluids almost exclusively for caloric intake, using dDAVP may quickly cause fluid overload and hyponatremia,[68,72] especially when administered orally.[73] Buccally-administered intranasal or subcutaneous dDAVP can be diluted into smaller doses, which lowers the risk of serum sodium fluctuations.[8,72–74] However, many providers choose thiazide diuretics for infants. Thiazide diuretics, in combination with low renal solute formula, breast milk, which is naturally low in solute, or amiloride, optimize serum osmolality management.[68,72,75] Infants treated with thiazide diuretics may develop slow weight gain and hypercalcemia.[75,76] Desmopressin lyophilizate, a newer treatment, melts sublingually and has greater bioavailability than dDAVP tablets with comparable efficacy, but may cost more.[77,78] Smaller doses make it a potential treatment option for infants.[8,79]

Adipsic central DI should be managed with dDAVP and a fixed fluid regimen based on the child's weight.[4,8,44]

If nephrogenic DI cannot be managed with appropriate water and sodium intake, children may be treated with thiazide diuretics and secondary[68] nonsteroidal antiinflammatory drug (NSAID) or amiloride use.[80] NSAIDs increase proximal tubule water reabsorption when coupled with thiazides.[8] It may be effective because COX-2 is known to be upregulated in patients with nephrogenic DI.[81] However, because of the gastrointestinal side effects of NSAIDs and concerns for infant use, amiloride is favored.[68,80,82] Sildenafil citrate increases aquaporin-2 trafficking to the apical membrane and could be effective in certain genotypes.[83]

SIADH

Epidemiology

SIADH is one of the most prevalent causes of hyponatremia in children.[84] It is the major cause of euvolemic hyponatremia in children.[85] The prevalence of SIADH varies with etiology. For example, Seetharam et al[86] reported a prevalence of ∼10% in pediatric patients undergoing chemotherapy for acute lymphoblastic leukemia, whereas Hasegawa et al[87] reported a prevalence of ∼30% in hospitalized children with acute febrile illnesses.

Pathophysiology

Secretion of AVP outside an osmotic or nonosmotic stimulation is termed SIADH.[88] Elevated atrial natriuretic peptide levels[89] may compensate for the increased secretion of AVP and the resulting lowering of aldosterone, causing hyperosmolar urine and euvolemia.[12] Over time, the phenomenon of escape from antidiuresis occurs, in which oversecretion of AVP eventually downregulates V2 receptors and the aquaporin-2 channel.[90]

Etiology

The heterogeneity of SIADH is represented in its etiologies. Different classes of pharmacologic agents are associated with SIADH in children,[12] including antineoplastic agents,[91–93] anticonvulsants,[91,94] antidepressants,[91] antipsychotics, and pain medications.[91] Although some pharmacologic agents induce a hyponatremic state within hours,[93] SIADH secondary to selective serotonin reuptake inhibitors can develop a few days after

administration.[95] Shepshelovich et al[91] reported an increase in incidence but not severity of SIADH with concurrent use of multiple SIADH-associated drugs. Malignancies can result in ectopic or inappropriate endogenous AVP production,[12,96] most commonly lymphoma, Ewing sarcoma, and carcinoma of the lung, bladder, duodenum, pancreas, and thymus.[85] Surgeries can stimulate inappropriate AVP release in children from severe pain, nausea, general anesthesia, and direct tissue trauma in the case of neurosurgical procedures.[12,85]

Up to 20% of patients diagnosed with SIADH have less-than-expected AVP secretion for degree of hyponatremia,[97] which could be confirmed by serum copeptin. Thus, the inherited form of SIADH, nephrogenic SIADH, should be suspected in the child.[85] Additionally, nephrogenic SIADH should be in the differential diagnosis for infants with hyponatremia. Children affected by this disorder may present as infants with signs and symptoms of SIADH, despite less AVP secretion than what is found in central SIADH.[97] It is an X-linked disorder caused by a mutation in the V2 receptor rendering it constitutively active.[12,95,97] Biebermann et al[98] recently reported a novel missense mutation of *GNAS* in 2 pediatric patients presenting with multisystem disease including nephrogenic SIADH.

Differential Diagnosis

Up to 20% of hospitalized children may have hyponatremia, defined as serum sodium levels <135 mEq/L.[99] Others propose a wide range in prevalence between 1.4% and 45%, depending on the inclusion criteria for hyponatremia. Children and neonates are more likely to develop hospital-acquired hyponatremia than present with it.[84,100]

Causes of hyponatremia can be divided into states of fluid load: hypovolemia, euvolemia, and hypervolemia. Cerebral salt wasting is a prevalent cause of hypovolemic hyponatremia in children,[85] often because of traumatic brain injury or neurosurgical procedures.[101] In cerebral salt wasting, excessive sodium excretion may be due to reduced sodium reabsorption secondary to impaired sympathetic innervation,[12,95] whereas the role of atrial natriuretic peptide remains controversial.[12,95,101] Other causes of hypovolemic hyponatremia are gastrointestinal conditions, such as gastroenteritis, severe burns, and acute sequestration into third spaces including sepsis.[85] A urine sodium concentration <10 mEq/L differentiates these conditions from cerebral salt wasting, which has a urine sodium concentration >20 mEq/L.[85]

Hypervolemic hyponatremia occurs in congestive heart failure, cirrhosis, and nephrotic syndrome.[12,85] The hypervolemia manifests in extravascular edema.[12] Reduced effective circulating volume stimulates AVP secretion.[12]

Other causes of hyponatremia in children include ecstasy and other substances, which initiate inappropriate secretions of AVP, and endurance exercise from sweating and high fluid intake.[102]

Clinical Signs and Symptoms

SIADH is characterized by euvolemic hyponatremia in the presence of impaired urinary dilution.[12] SIADH is usually transient[97] in pediatric patients but may be chronic when secondary to CNS or pulmonary conditions.[85] Severe hyponatremia can cause hyponatremic encephalopathy,[102,103] with seizures, coma, paralysis, and even death, as excess water diffuses via an osmotic gradient into brain cells.[85] Furthermore, children have a higher likelihood of brain herniation with hyponatremia because of their larger brain-to-skull volume ratio.[12]

It remains difficult to distinguish between cerebral salt wasting and SIADH. Children with CNS disease may be more likely to have cerebral salt wasting than SIADH.[104] In postoperative hyponatremic states, age <7 years, and female sex were associated with cerebral salt wasting versus SIADH.[105] Clinical signs and symptoms of cerebral salt wasting in children include polyuria, hypovolemia, hyponatremia, and elevated potassium excretion.[101] Signs of dehydration in children, including dry mucous membranes, poor skin turgor, and a sunken fontanelle in infants, should raise suspicion for cerebral salt wasting.[12,106] It is typically transient in children, lasting 10 to 20 days.[101]

Diagnostic Criteria

Differentiating cerebral salt wasting from SIADH can be particularly difficult in children. Low urine output in children suggests SIADH over cerebral salt wasting.[106] SIADH is a diagnosis of elimination, but essential criteria exist.[103] Supplemental criteria raise clinical suspicion for SIADH in children if not all essential criteria are met. Elevated fractional uric acid excretion has been used in adults with SIADH to differentiate it from cerebral salt wasting, but this trend is not confirmed in children.[12,107] Serum copeptin is thought to have low diagnostic value in hyponatremia, given the breadth of conditions causing hyponatremia.[66] Hypovolemia in cerebral salt wasting typically presents with a high urine output, tachycardia, hypotension, increased SUN, creatinine, and serum uric acid concentrations.[85,102] Normal fractional uric acid excretion in the clinical setting of mild hyponatremia is highly suggestive of reset osmostat SIADH, a condition in which a smaller physiologic stimulus than normal is the threshold for AVP secretion.[12,108]

Treatment

With many hospitalized children at risk for hyponatremia, prevention

with isotonic maintenance fluids is important.[85]

If hyponatremia presents with neurologic manifestations, it should be managed with hypertonic saline and serial monitoring of serum sodium.[12] Reversal of hyponatremia needs to be monitored carefully to prevent overcorrection and ensuing demyelination.[109]

First-line therapy of SIADH is fluid restriction,[85] particularly postoperatively.[110,111] However, fluid restriction is burdensome on infants because they rely on fluid intake for calories; higher caloric milk concentrations are often useful.[97] Other management options are pharmacologic agents (Tables 4 and 5).[112] In a prospective study on adults with SIADH, researchers found oral urea to be similarly tolerated and effective when compared with vaptans.[113] Vaptans are approved for euvolemic and hypervolemic hyponatremia in adults.[114] Both tolvaptan, the oral form, and conivaptan, the intravenous form, have been used to manage SIADH in pediatric patients, as reported in case studies; however, more research is required to study the efficacy and safety in children.[106,107,115,116] For drug-induced SIADH, cessation of the causative agent may suffice.

Nephrogenic syndrome of inappropriate antidiuresis may be treated with demeclocycline, lithium, and other pharmacologic agents that antagonize the mechanism of action of the V2 receptor.[95,97] However, these agents are falling out of favor in pediatrics because of other therapeutic options.[85]

Hypovolemic and hypervolemic hyponatremia can be managed with isotonic fluids and diuretics with fluid restriction, respectively.[85]

TABLE 5 Pathophysiology of DI and SIADH

	Central DI	SIADH
Secretion of AVP	Decrease	Increase
Insertion of aquaporin-2 channel in collecting ducts	Decrease	Increase
Effect on water reabsorption	Decrease	Increase
Resulting plasma sodium concentration	Increase	Decrease

SPECIAL CONSIDERATIONS FOR ACUTE POSTOPERATIVE VASOPRESSIN ABNORMALITIES

Neurosurgical procedures in children can acutely disrupt vasopressin secretion, often in a triple response consisting of transient DI, subsequent SIADH, and a final phase of DI or a return to normal AVP release.[117] Postsurgical edema or perioperative trauma causes axonal shock, resulting in the initial central DI phase, lasting up to 2 days.[37,41,118] The second SIADH phase, lasting 2 to 10 days, occurs from atrophying cells releasing stored AVP.[41] The final phase of permanent DI occurs if >80% of magnocellular neurons were injured and thus cannot form new AVP. Kruis et al[37] reported a triple response in 22.5% of children undergoing surgery in the sellar area. In children, increased surgery time likely raises the risk of developing a triphasic response.[119] Risk factors for permanent postoperative DI in children include early onset of the triphasic response, complications independent of osmoregulation, and large fluctuations in postoperative serum sodium.[37] Treating initial DI with vasopressin may mask the transition to SIADH,[41] which is why some providers prefer exclusive fluid administration initially.[120] During the SIADH phase, fluid restriction may suffice; however, a single tolvaptan dose for children may be needed for severe hyponatremia.[111,120] Also, even children with preoperative DI can still experience the triple phase.[37] Children undergoing surgery in the sellar area need to be closely monitored for changes in serum osmolality to prevent acute shifts in serum sodium concentration.

TABLE 4 Review of Pharmacologic Therapy for SIADH

Therapy	Typical Dose	Mechanism of Action
Furosemide[112,158]	0.5–2 mg/kg dose	Loop diuretic that blocks sodium, chloride, and potassium reabsorption and improves free water excretion
Oral urea[159]	0.1 g/kg per d (in 4 doses) Maximum dose of 2 g/kg per d or total dose of 60 g/d	Decreases natriuresis and enhances free water excretion
Vaptans[85,a]	Tolvaptan: 0.14–0.28 mg/kg/d (from alternate days to up to 2 doses)[106,107] 0.22–0.8 mg/kg/d[115] Conivaptan: 10–30 mg/d (continuous administration over 24 h)[116]	Competitively bind V2 receptor, blocking the insertion of the aquaporin-2 channel, enhancing urine dilution, and improving serum sodium
Demeclocycline, lithium[85,a,b]	—	Antagonize the V2 receptor
SGLT-2 Inhibitor[160,a]	—	Increases glucosuria and free water clearance

—, not applicable.
[a] Pediatric dosing not fully established.
[b] Not recommended for use in children because of adverse side effects.

FUTURE DIRECTION

Further genetic testing and improved understanding of genotype and phenotype correlations in different AVP-associated mutations may improve clinical management of various subpopulations of DI.[121] For

example, Patti et al[121] recently described a single nucleotide variant in the *AVP NPII* gene predicting later DI onset at a median of 120 months. Greater use of molecular analysis has the potential to enhance genetic counseling and diagnostic accuracy while limiting the use of unnecessary testing.

Copeptin holds promise for improving identification and diagnosis in children with hyper- and hypoosmolar states. Further work is needed to establish pediatric references ranges throughout childhood. Serum copeptin concentrations coupled with the hypertonic saline infusion rather than the water deprivation test could improve diagnostic accuracy of polyuria-polydipsia syndrome and remove the burden of the water deprivation test; however, close monitoring would be needed in the pediatric population. Postoperative copeptin values may promote earlier recognition and diagnosis of DI. In adults, low postoperative copeptin values predicted DI onset.[122] Similar pediatric studies are needed, including those using intraoperative copeptin to predict DI or indicate shifts in the triphasic response, allowing physicians to change management preemptively.

Point-of-care sodium devices are needed to help parents and children better monitor fluctuations at home, especially in children with adipsia and DI.[123] With caregiver education on use of the device, proper interpretation of results, and appropriate subsequent management, expansion of at-home point-of-care sodium may reduce burden on the health care system and improve patient outcomes. Green et al found a strong correlation between point-of-care sodium analyzer and laboratory sodium values. Additionally, use of at-home devices resulted in appropriate treatment outcomes in >90% of cases of DI.[124]

CONCLUSIONS

Pediatric vasopressin-dependent disorders remain challenging to diagnose and treat. Early recognition and prompt management of DI and SIADH can improve quality of life and reduce potential risks associated with serum sodium concentration abnormalities. Improved diagnostic tools, such as identification of genetic markers, copeptin, and point-of-care sodium could give providers insight into disease progress and prognosis, moving toward better outcomes and quality of life for children and their families.

ABBREVIATIONS

AVP: arginine vasopressin
CNS: central nervous system
dDAVP: deamino-8-D-arginine vasopressin
DI: diabetes insipidus
NSAID: nonsteroidal antiinflammatory drug
SIADH: syndrome of inappropriate secretion of antidiuretic hormone
SUN: serum urea nitrogen
V2 receptor: vasopressin-2 receptor

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