Published in final edited form as:

Endocrinol Metab Clin North Am. 2009 December ; 38(4): 663–672. doi:10.1016/j.eccl.2009.08.002.

Pediatric Disorders of Water Balance

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Synopsis

Fluid homeostasis requires adequate water intake, regulated by an intact thirst mechanism, and appropriate free water excretion by the kidneys, mediated by appropriate secretion of arginine vasopressin (AVP) [also known as antidiuretic hormone (ADH)]. AVP exerts its antidiuretic action by binding to the X chromosome-encoded V2 vasopressin receptor (V2R), a G-protein coupled receptor on the basolateral membrane of renal collecting duct epithelial cells. Following V2R activation, increased intracellular cAMP mediates shuttling of the water channel aquaporin 2 (AQP-2) to the apical membrane of collecting duct cells, resulting in increased water permeability and antidiuresis. Clinical disorders of water balance are common, and abnormalities in many steps involving AVP secretion and responsiveness have been described. The focus of this chapter is on the principal disorders of water balance, diabetes insipidus (DI) and the Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH).

Keywords

hyponatremia; hypernatremia; diabetes insipidus; SIADH

Pediatric Disorders of Water Balance

Under normal circumstances plasma osmolality is maintained within a relatively narrow range (280-295 mOsm/kg). This homeostasis requires adequate water intake regulated by an intact thirst mechanism and appropriate free water excretion by the kidneys, mediated by appropriate secretion of arginine vasopressin (AVP) [also known as antidiuretic hormone (ADH)]. AVP is produced by a subset of magnocellular neurons in the paraventricular nuclei (PVN) and supraoptic nuclei (SON) of the hypothalamus. Axons from these neurons project via the pituitary stalk to the posterior pituitary gland. ¹ The terminals of these axons contain neurosecretory granules that store AVP for release. ² A gene on chromosome 20p13 encodes both AVP and its carrier protein, Neurophysin II (NPII). AVP and NPII are synthesized as a single polypeptide, cleaved within the neurosecretory granules and

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reassembled into AVP/NPII complexes prior to secretion.³ Stores of preformed AVP in the posterior pituitary can last for 30 to 50 days under basal circumstances, or for 5 to 10 days during maximal stimulation.⁴ This significant storage capacity explains why a defect in AVP synthesis may not become clinically apparent until weeks after a causal insult, and a partial defect may only be revealed after prolonged water deprivation.

AVP synthesis, transport, and secretion are regulated primarily by changes in plasma osmolality, and to a lesser degree, by changes in circulating volume.^{1, 5} Osmoreceptors in the hypothalamus (organum vasculosum of the lamina terminalis, OVLT and anterior hypothalamus) stimulate secretion of AVP when plasma osmolality increases by as little as 1% in healthy individuals. Basal AVP levels are normally low, 0.5 to 2 pg/ml, and do not increase until plasma osmolality exceeds 280 mOsm/kg.² Maximum urine concentration (urine osmolality 900 to 1200 mOsm/kg) is attained at plasma AVP levels of 5 to 6 pg/ml. Although plasma AVP can continue to rise above 6 pg/ml with ongoing plasma hyperosmolality, further increases in urine osmolality cannot be achieved due to limits of the renal medullary gradient.² Changes in blood volume inversely affect AVP secretion such that a decrease in circulating blood volume by 8 to 10% stimulates AVP secretion, and increases in intravascular volume inhibit AVP release.⁶ Baroreceptors in the carotid sinus and aortic arch ("high pressure baroreceptors"), and in the atria and pulmonary venous circulation ("low pressure baroreceptors") relay pressure and volume information via the glossopharyngeal and vagus nerves, respectively, to the brain stem. These baroreceptors become activated when stretched by increases in intravascular volume, leading to inhibition of AVP secretion through fibers projecting from the brain stem to the PVN and SON of the hypothalamus.⁶ In addition, a variety of other factors affect AVP secretion. AVP secretion is stimulated by pain, nausea, stress, and a variety of drugs and is inhibited by multiple factors.^{2, 6}

Adequate water intake, governed by an intact thirst mechanism, is also regulated predominantly by changes in plasma osmolality, as well as by changes in intravascular volume and blood pressure. Thirst is consistently stimulated when plasma osmolality increases by 2 to 3 % or circulating blood volume decreases by 4 to 10%.^{2, 7} Since the thresholds that trigger thirst are higher than those that trigger AVP secretion, adequate thirst becomes essential during pathologic states of AVP deficiency or insensitivity.² Challenges in the management of adipsic diabetes insipidus, resulting from damage to thirst centers as well as to AVP-secreting neurons, highlight the critical role of thirst in the maintenance of plasma osmolality when AVP secretion or responsiveness is inadequate.

AVP exerts its antidiuretic action by binding to the X-chromosome-encoded V2 vasopressin receptor (V2R), a G-protein coupled receptor on the basolateral membrane of renal collecting duct epithelial cells. Following V2R activation, increased intracellular cAMP mediates shuttling of the water channel aquaporin 2 (AQP-2) to the apical membrane of collecting duct epithelial cells, resulting in increased water permeability and antidiuresis.⁸ (Figure 1)

Clinical disorders of water balance are common, and abnormalities in many steps involving AVP secretion and responsiveness have been described. The focus of this review is on the

principal disorders of water balance, diabetes insipidus (DI) and the Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH).

Diabetes Insipidus

Diabetes insipidus (DI) results from the inability to reabsorb free water. Polyuria, polydipsia, and hypo-osmolar urine are the hallmarks of this disorder, though hypernatremia may be present, particularly in infants, at the time of diagnosis. DI can be central, due to deficiency of AVP, or nephrogenic, due to a defect in AVP action in the kidneys.^{9, 10} (Table 1).

Nephrogenic DI (NDI) may be genetic or acquired. The genetic causes are inactivating mutations of the *AVPR2* gene, located on the X chromosome (Xq28), or autosomal recessive or dominant mutations in the *AQP2* gene, located on chromosome 12 (12q13). Acquired NDI can be caused by a variety of conditions including some forms of primary renal disease, obstructive uropathy, hypokalemia, hypercalcemia, sickle cell disease, and drugs such as lithium and demeclocycline.^{2, 9-11} Prolonged polyuria of any cause can also lead to some degree of NDI due to a reduction of tonicity in the renal medullary interstitium and a subsequent decrease in the gradient necessary to concentrate urine.

X-linked NDI (XNDI) is rare, affecting approximately 4 in 1,000,000 males worldwide, and accounts for about 90% of the genetic causes of NDI. Of the 211 reported *AVPR2* mutations causing XNDI, approximately half are missense, and 31 of these have been characterized functionally.¹² Most *AVPR2* missense mutations result in a translated but misfolded V2R protein that remains trapped in the endoplasmic reticulum.¹³⁻¹⁵ Pharmacological chaperones can partially rescue the cell-surface expression and functional activity of misfolded mutant V2Rs that would otherwise be targeted for degradation.¹⁶⁻¹⁸

Infants with congenital (X-linked or autosomal) NDI typically present within the first several weeks of life with non-specific symptoms such as fever, vomiting, dehydration and growth failure, associated with polyuria and hypo-osmolar urine (50-100 mOsm/kg). Mental retardation of variable severity and intracerebral calcifications of the frontal lobes and basal ganglia can result from repeated episodes of dehydration if the condition remains untreated.¹⁹ Longstanding polyuria and polydipsia can lead to nonobstructive hydronephrosis, hydroureter and megabladder.^{20, 21} Thiazide diuretics with low sodium intake were historically used to treat NDI²² as this combination decreases glomerular filtration rate, resulting in decreased urine output. Over the last 20 years, thiazide diuretics in combination with either amiloride or indomethacin have become the mainstay of congenital NDI treatment.^{19, 23, 24} More recently, in vitro studies have demonstrated that pharmacologic chaperones, which are cell-permeable, non-peptide small molecules, can restore the cell-surface expression and function of misfolded mutant V2Rs.^{16-18, 25} One such compound is orally-active, well-tolerated and effective in decreasing urine volume in adults with severe XNDI.^{18, 26} Thus, pharmacologic chaperones represent a new, safe, and targeted therapy for XNDI caused by protein-misfolding due to missense mutations of *AVPR2*.

Central DI is rarely congenital and more frequently acquired. Congenital central DI may be caused by structural malformations affecting the hypothalamus or by autosomal dominant or recessive mutations in the gene encoding AVP/NPII. The autosomal dominant causes are more common and result from heterozygous *AVP/NPII* gene mutations.³ The proposed mechanism for the dominant negative effect is that the heterozygous mutation disrupts the processing of the mutant precursor.^{27, 28} The accumulation of this misfolded protein in the vasopressinergic neurons causes a gradual destruction of these neurons.^{3, 27} In such patients, clinical DI usually develops several months to years after birth. A rare autosomal recessive form of central DI has been reported in association with a mutation in the *AVP/NPII* gene resulting in a biologically inactive AVP.²⁹

Acquired forms of central DI occur in association with a variety of disorders in which there is destruction or degeneration of vasopressinergic neurons. Etiologies include primary tumors (e.g. craniopharyngioma, germinoma) or metastases, infection (meningitis, encephalitis), histiocytosis, granuloma, vascular disorders, autoimmune disorders (lymphocytic infundibuloneurohypophysitis), and trauma or surgery.^{9, 10, 30} Idiopathic DI is a diagnosis of exclusion, and one that is made with decreasing frequency due to improved sensitivity of brain MRI imaging and of cerebral spinal fluid (CSF) and serum tumor markers.^{30, 31}

The principal presenting sign of DI is polyuria, which in addition to deficiency or impaired responsiveness to AVP, may result from an osmotic agent (e.g. hyperglycemia in diabetes mellitus) or from excessive water intake (primary polydipsia). Hypernatremia usually does not occur if patients have an intact thirst mechanism, adequate access to fluids, and no additional ongoing fluid losses (e.g. diarrhea). Infants with DI, in addition to polyuria and polydipsia, may be irritable and have fever of unknown origin, growth failure secondary to inadequate caloric intake, and hydronephrosis. Older children may also have nocturia and enuresis. DI may not be apparent in patients with coexisting untreated anterior pituitary-mediated adrenal glucocorticoid insufficiency, as cortisol is required to generate normal free water excretion.²

A diagnosis of DI can be made if simultaneous screening laboratory studies reveal hyperosmolality concurrent with urine that is inappropriately dilute. If DI is present, it is more likely to be uncovered by these screening tests if they are obtained as soon as possible after awakening, and prior to any fluid intake (assuming the patient has not consumed fluids overnight). However, since most patients with DI have intact thirst and can drink to prevent hyperosmolality and hypernatremia, a standardized water deprivation test is often necessary to make the diagnosis. The patient is monitored with serial measurements of weight, serum sodium, serum osmolality, urine volume, and urine osmolality while being fasted and deprived of water for 8 to 10 hours. If urine osmolality > 750 mOsm/kg is achieved with any degree of water deprivation, DI can be excluded.^{6, 9} The diagnosis of DI is established if serum osmolality rises above 300 mOsm/kg and urine osmolality remains below 300 mOsm/kg. Urine osmolality in the 300-750 mOsm/kg range during water deprivation may indicate partial DI.⁹ If DI is suspected, a plasma sample should be obtained for AVP radioimmunoassay. AVP or a synthetic analog (desmopressin) should then be administered to distinguish AVP deficiency from AVP unresponsiveness.

Magnetic resonance imaging (MRI) of the brain, with particular attention to the hypothalamic-pituitary region is indicated in patients with central DI. The posterior pituitary hyperintensity ("bright spot") on T1-weighted MR images is often absent in central DI.^{30, 32-35} However, the bright spot can be absent in normal individuals³⁶, and conversely, children with central DI can have a normal bright spot at the time of diagnosis.³⁷⁻³⁹ Therefore, the presence of the bright spot does not establish neurohypophyseal integrity, and its absence does not always indicate CNS pathology. In central DI patients with or without the posterior pituitary bright spot, an otherwise normal MRI warrants close follow-up with CSF tumor markers and cytology, serum tumor markers, and serial contrast-enhanced brain MRIs for early detection of an evolving occult hypothalamic-stalk lesion.³¹

The management of central DI includes treating the primary disease, correction of a fluid deficit, if present, and normalization of urine output with desmopressin. This AVP analog has markedly reduced pressor activity in comparison to native AVP, has a prolonged half-life, and can be administered orally, intranasally, or by subcutaneous injection. In infancy, if polyuria is not excessive, DI may be best managed with fluid intake alone in order to avoid a potential risk of hyponatremia with desmopressin treatment.

Syndrome of Inappropriate ADH secretion (SIADH)

SIADH, caused by the inability to excrete free water, is characterized by hyponatremia and hypoosmolality with inappropriately concentrated urine and natriuresis.⁴⁰⁻⁴² Following from the original criteria established by Bartter and Schwartz⁴⁰ a diagnosis of SIADH is made when the following occur: 1) plasma hypo-osmolality (< 275 mOsm/kg); 2) less than maximally dilute urine (urine osmolality > 100 mOsm/kg); 3) euvolemia (secondary to regulatory adaptations); 4) natriuresis; 5) normal renal function; and 6) no evidence of thyroxine or cortisol deficiency. While most patients with SIADH have inappropriately measurable or elevated levels of plasma AVP relative to plasma osmolality, 10-20% of patients with SIADH do not have measurable AVP levels. This may reflect issues of assay sensitivity or may indicate a syndrome resembling SIADH, such as the recently described Nephrogenic Syndrome of Inappropriate Antidiuresis (NSIAD) associated with an activating mutation in the X-linked G-protein-coupled V2R and unmeasurable circulating levels of AVP.⁴³

Euvolemia in chronic SIADH is an important distinguishing factor in the evaluation of a patient with serum hypoosmolality, and has a bearing on treatment issues, as will be discussed subsequently. Euvolemia in chronic SIADH is thought to represent an adaptation to water overload. This adaptation is mediated, in part, at the cellular level through depletion of intracellular electrolytes (potassium) and organic osmolytes.⁴¹ The loss of brain solutes is thought to allow effective regulation of brain volume during chronic hyponatremia and SIADH. Natriuresis, thought to be mediated in part through secretion of atrial natriuretic peptide, also contributes to volume regulation in chronic SIADH.⁴⁴ Cerebral salt wasting (CSW), associated with some intracranial diseases (e.g. subarachnoid hemorrhage), is often considered in the differential diagnosis of SIADH. However, the hypoosmolality, hyponatremia and natriuresis in CSW are associated with volume contraction, which distinguishes this disorder from the euvolemic condition of SIADH.⁴¹

A large number of disorders and conditions are associated with SIADH, and can be grouped into five categories (Table 2): 1) neurological and psychiatric disorders; 2) a large variety of drugs (e.g. phenothiazines, tricyclic antidepressants); 3) a variety of pulmonary disorders and interventions (e.g. pneumonia, asthma, positive pressure ventilation); 4) non-CNS tumors with ectopic production of AVP; and 5) miscellaneous causes (e.g. AIDS, post-operative state, glucocorticoid deficiency, severe hypothyroidism).^{41, 42}

Therapy for SIADH includes treatment of the underlying disorder (or discontinuation of an offending drug) and fluid restriction. Replacement of sodium losses may also be necessary, but can usually be achieved through normal dietary salt intake. Severe hyponatremia (serum sodium < 120 mEq/L) may be associated with CNS abnormalities, including seizures, and may require treatment with hypertonic (3%) intravenous sodium chloride solution.

Concurrent use of a diuretic, such as furosemide, may be indicated when volume expansion is severe. Other therapeutic approaches include the use of agents which induce NDI, such as demeclocycline and lithium, although both are contraindicated particularly in younger pediatric patients because of untoward side effects. Urea has been used as an osmotic diuretic in pediatric SIADH and in NSIAD.⁴⁵ A variety of non-peptide V2R antagonists are in various stages of clinical trials or have been approved by the FDA for use in adults.⁴¹

If SIADH and hyponatremia are acute (< 48 hours), it is thought that hyponatremia can be corrected quickly. However, if SIADH and hyponatremia are chronic (>48 hours), overzealous treatment can result in CNS damage, including central pontine myelinolysis (CPM).⁴¹ Brain solute loss, while an important regulatory mechanism in chronic SIADH, may predispose to the development of CPM with rapid correction of serum osmolality. It is generally recommended that plasma sodium be corrected to a “safe” level of approximately 120-125 mEq/L at a rate of no greater than 0.5 mEq/L per hour with an overall correction that does not exceed 12 mEq/L in the initial 24 hours and 18 mEq/L in the initial 48 hours of treatment.⁴¹

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Figure 1.

Antidiuretic action of AVP on the renal collecting duct epithelial cell. AVP binding to the V2R, located on the basolateral membrane, results in an increase in cAMP and activation of protein kinase A (PKA). Ser-256 on the C-terminal of AQP-2 is phosphorylated by PKA, resulting in the shuttling of AQP-2 to the apical membrane, allowing the normally impermeable apical membrane to become permeable to water. In addition, acting through a cAMP-response element in the AQP-2 promoter, chronic exposure of these cells to AVP results in increased synthesis of AQP-2. AQP-3 and AQP-4, constitutively located on the basolateral border of the collecting duct membrane, provide channels for the transport of water out of the collecting duct cells and into the interstitium and circulation. Modified from Prog Biophys Mol Biol, Schrier RW et al. Renal aquaporin water channels: from molecules to human disease 2003; 81:117-131, with permission from Elsevier.

Table 1**Causes of DI**

Central DI
Congenital
Structural malformations affecting the hypothalamus/pituitary
Autosomal dominant (or rarely recessive) mutations in gene encoding AVP/NPII
Acquired
Primary tumors or metastases
Infection (e.g. meningitis, encephalitis)
Histiocytosis
Granulomatous diseases
Autoimmune disorders (lymphocytic infundibuloneurohypophysitis)
Trauma
Surgery
Idiopathic
Nephrogenic DI
Congenital
X-linked: inactivating mutations in <i>AVPR2</i>
Autosomal: recessive or dominant mutations in <i>AQP-2</i>
Acquired
Primary renal disease
Obstructive uropathy
Metabolic causes (e.g. hypokalemia, hypercalcemia)
Sickle cell disease
Drugs (e.g. lithium, demeclocycline)
Prolonged polyuria of any cause

Table 2
Causes of SIADH

-
- 1** Neurological and psychiatric disorders
    - a. Infections: meningitis, encephalitis, brain abscess
    - b. Vascular: thrombosis, subarachnoid or subdural hemorrhage, temporal arteritis, cavernous sinus thrombosis, stroke
    - c. Neoplasm: primary or metastatic
    - d. Skull fracture, traumatic brain injury
    - e. Psychosis, delirium tremens
    - f. Other: Guillain-Barré syndrome, acute intermittent porphyria, autonomic neuropathy, postpituitary surgery, multiple sclerosis, epilepsy, hydrocephalus, lupus erythematosus.
  - 2** Drugs
    - a. Intravenous cyclophosphamide
    - b. Carbamazepine
    - c. Vincristine or vinblastine
    - d. Thiothixene
    - e. Thioridazine, other phenothiazines
    - f. Haloperidol
    - g. Amitriptyline, other tricyclic antidepressants or serotonin-reuptake inhibitors
    - h. Monoamine oxidase inhibitors
    - i. Bromocriptine
    - j. Lorcaïnide
    - k. Clofibrate
    - l. General anesthesia
    - m. Narcotics, opiate derivatives
    - n. Nicotine
    - o. Desmopressin overtreatment of DI or enuresis
  - 3** Lung diseases and interventions
    - a. Pneumonia
    - b. Tuberculosis
    - c. Lung abscess, empyema
    - d. Acute respiratory failure
    - e. Positive pressure ventilation
  - 4** Non-CNS tumors with ectopic production of AVP
    - a. Carcinoma of lung, (small cell, bronchogenic), duodenum, pancreas, thymus, olfactory neuroblastoma, bladder, prostate, uterus
    - b. Lymphoma
    - c. Sarcoma
    - d. Leukemia
  - 5** Miscellaneous
    - a. AIDS
    - b. Post-operative state
    - c. Glucocorticoid deficiency
    - d. Hypothyroidism

e. Idiopathic

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