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November 2024
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Understanding Syndrome of Inappropriate Antidiuretic Hormone (SIADH) and Diabetes Insipidus (DI)

SIADH and DI are both disorders of water regulation affecting the activity or systemic release of anti-diuretic hormone (ADH). ADH secretion is normally inhibited in response to water intake. In SIADH, ADH is not suppressed, resulting in water retention and significant hyponatremia. In DI, there is either decreased production of ADH (central DI), or normal ADH secretion with resistance in the kidneys to its effects (nephrogenic DI). The net result of DI is large-volume diuresis of dilute urine which causes dehydration and hypernatremia.

Pathophysiology

To best understand these complex syndromes, a sound knowledge of the underlying physiology is essential. The kidneys have an important role in fluid and electrolyte homeostasis. In general, homeostasis is achieved by adjustments to urine output and the electrolyte composition of urine and serum. Fluctuations occur with both intake or administration of fluid and solutes (salt, protein) into the body with subsequent hormonal response/feedback. The release of ADH [synonymous with the term arginine vasopressin (AVP)] by the posterior pituitary gland is regulated by a signaling network involving osmosensors, barosensors and volume sensors in the body.

In the renal system, these sensors are in the collecting ducts of the kidney; ADH is the key regulator of water absorption here. The pituitary gland is stimulated to secrete ADH when the body senses hypertonicity allowing the absorption of water back to circulation (or water retention) by means of increased water permeability and Na^+ absorption in the renal system thereby preventing diuresis (as the name ADH suggests). When this occurs, urine becomes more concentrated and urine output decreases. Alternately, when the body sense hypotonicity, ADH secretion is suppressed, allowing for a less concentrated and higher volume of urine output. ADH secretion also plays a role in the sensation of thirst.

Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH)

In SIADH, the body is unable to suppress the secretion of ADH, leading to impaired water excretion and reduced urine output. Normally, when water is ingested, serum tonicity and osmolality decrease and ADH is suppressed, resulting in output of a dilute (less concentrated) urine. This pathway is impaired in SIADH. Plasma osmolality falls, leading to dilutional hyponatremia.

Syndrome of Inappropriate Antidiuretic Hormone (SIADH)	
Potential etiologies (Sterns, 2024)	• CNS disturbances leading to increased ADH release (stroke, hemorrhage, infection, trauma) • Malignant tumor production of ADH (common in small cell carcinoma of the lung) • Drug-related ○ Includes but not limited to SSRIs, carbamazepine, chlorpropamide, cyclophosphamide

	○ Administration of hormones such as vasopressin and desmopressin to treat other medical conditions • Surgery • Pulmonary disease ○ Pneumonia; less frequently asthma, respiratory failure, atelectasis, pneumothorax • Hormone deficiency (hypopituitarism, hypothyroidism) • HIV • Hereditary • Idiopathic *NOTE: There is a condition called cerebral salt wasting which may mimic SIADH, but this condition leads to volume depletion, causing a secondary elevation in ADH.*
Clinical manifestations Signs and symptoms depend on the severity of hyponatremia and the rate at which it develops. If the sodium level has decreased slowly over a long period, the patient may be asymptomatic.	**Hyponatremia** • Severe (Na^+ less than 120 mEq/L) ○ seizures, poor concentration, weakness, hyperreflexia, headache, speech difficulties, coma, cerebral edema • Moderate (Na^+ 120-129 mEq/L) ○ dizziness, gait disturbance, restlessness, headache, confusion, forgetfulness, lethargy, or may present asymptomatic • Mild (Na^+ 130-135 mEq/L) ○ often asymptomatic *Note: SIADH may be persistent or transient depending on etiology*
Common laboratory trends	• Hyponatremia • Hypoosmolality (serum osmolality less than 280 mOsm/kg) • Urine osmolality greater than 100 mOsm/kg • Urine sodium typically greater than 40 mEq/L • Serum potassium – normal or low normal • Acid-base status – normal • Serum uric acid – low
Treatment	• Treatment of underlying condition/disease • Prevent further decline in serum Na^+ concentration • Goals of treatment may vary depending on clinical acuity and co-morbidities • Key component of treatment is correcting hyponatremia ○ Fluid restriction ○ Salt administration (increases solute excretion and urine volume leading to increased Na^+) ▪ May be administered with loop diuretics which lowers urine osmolality and increases water excretion

	○ Vasopressin receptor antagonists ○ Saline or hypertonic saline (3%) in severe, symptomatic hyponatremia ○ Urea administration (increases solute excretion and urine volume leading to increased Na^+) **Persistent SIADH requires ongoing therapy.*
Na^+ correction rates	Hyponatremia MUST be corrected slowly. Rapid correction could lead to cerebral fluid shifts and rarely, a life-threatening complication called osmotic demyelination syndrome (ODS). • In general, rate of correction should 4-6 mEq/L in the first 24 hours and should always be less than 8 mEq/L during this critical period. • In those with severe neurologic symptoms, correction rate may be faster, 4-6 mEq/L in the initial 2- to 4-hour period to prevent further neurologic deterioration. • Na^+ should be checked every 2 to 3 hours during initial management and every 4 to 6 hours until Na^+ is 130 or greater.

Diabetes Insipidus

There are two major types of DI: central (also referred to as neurogenic or neurohypophyseal) and nephrogenic. The common clinical manifestation of the two subtypes is polyuria. In general, polyuria is defined as urine output greater than 3 L/day in adults and greater than 2 L/day in children. Normal expected urine output in adults is 0.8-2 L/day; in severe cases of DI, 24-hour urine output could reach up to 10-20 L/day. A less common type of DI is *gestational DI* which is caused by increased metabolism of ADH by the placenta, leading to relative serum ADH deficiency. Regardless of etiology, DI causes dehydration unless fluid intake can keep up with urinary volume losses.

Diabetes Insipidus		
	Central DI	**Nephrogenic DI**
Mechanism	Insufficient ADH due to problem with production at the level of the hypothalamus or secretion at the posterior pituitary gland.	ADH secretion/production is normal but kidneys are resistant to the water retaining effects of the hormone.
Potential Etiologies (Bichet, 2023)	• Idiopathic • Autoimmune-mediated • Pituitary gland/hypothalamus damage due to trauma, surgery or hypoxic or ischemic encephalopathy • Familial • ADH-producing cells	• Mild cases driven by renal disease; typically asymptomatic, common in older adults with aging kidneys and loss of ability to concentrate urine • Congenital ○ Hereditary due to genetic defects, most typically presents in childhood • Acquired ○ Chronic lithium use ○ Metabolic conditions

		▪ Hypercalciuria ▪ Hypokalemia ▪ Obstructive uropathy ▪ Craniopharyngioma surgery

Clinical Manifestations	• Polyuria (possibly nocturia)
	• Polydipsia
	• Urine output greater than 50 mL/kg/day
	• Hypernatremia
	• Urine osmolality less than serum osmolality
	• May be partial or complete with range of symptoms
	  ○ Complete: urine output may reach 10-20 L/day
	• Clinical signs of dehydration (weight loss, irritability, headache, fatigue, dry skin, and mucous membranes)
	• In congenital cases, may present as failure to thrive during infancy
	• Onset of symptoms
	  ○ Abrupt in central DI
	  ○ Gradual in nephrogenic DI	

Diagnosis	• Evaluation of symptoms and laboratory abnormalities
	• Fluid restriction test/water restriction test leads to induced dehydration
	1. Measure body weight, plasma osmolality, serum sodium, urine volume and urine osmolality hourly.
	2. Stop when body weight decreased by 5% OR plasma osmolality/ sodium at upper limit of normal (ULN).
	3. If urine osmolality less than 300 mOsm/kg with hyperosmolality, administer desmopressin (0.03 μg/kg subcutaneously).
	  a. Repeat urine osmolality in 1-2 hours.
	4. Interpretation:
	  a. An increase in urine osmolality by 50% is seen with severe central DI.
	  b. No change, or less than 50%, suggests nephrogenic DI.
	  c. May be helpful to measure ADH levels before and after fluid restriction to distinguish between central and nephrogenic DI.	

Treatment	Desmopressin (DDAVP) • 1-2 μg subcutaneously daily BID • 2 μg intravenously given over two minutes • 10-20 μg via nasal spray BID-TID • 100-400 μg PO BID-TID • Recommendation to drink to thirst	• Thiazide diuretic and/or amiloride • Low sodium diet • Prostaglandin synthesis inhibitors (indomethacin)

Laboratory Findings

Typical Laboratory Findings		
	SIADH	**DI**
Serum osmolality	Decreased (less than 275mOsm/L)	Increased
Urine osmolality	Increased (concentrated urine [greater than 100 mOsm/L])	Decreased (less than serum osmolality)
Serum [Na^+]	Decreased	Increased (serum Na^+ greater than 142 mEq/L due to water loss)
Urine [Na^+]	Increased (greater than 40mEq/L)	Decreased (less than 30 mEq/L)
ADH	Increased	Decreased in central DI; normal in nephrogenic DI
Total body water (TBW)	Increased	Decreased
Urine volume/output	Decreased	Significantly increased
Volume status	Increased (euvolemic or hypervolemic)	Decreased (euvolemic or hypovolemic)

Nursing Considerations

Goals of care:

- Maintain adequate tissue perfusion and normal electrolyte levels
- Ensure patient understanding of treatments and fluid intake/dietary considerations
- Monitor for and prevent complications such as fluid overload, electrolyte abnormalities, and seizures

Nursing Assessments

- Hydration status: vital signs, orthostatic vitals, tissue perfusion
- Cardiac: rate or rhythm abnormalities
- Neuro: mental status, seizure activity, general neuro checks
- GU: urine characteristics (dilute vs concentrated)

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