SIADH, DI and Cerebral Salt Wasting

Karim Rafaat, MD
ADH

- ADH is produced in cells in the supraoptic and paraventricular nuclei.
- It is transported to and released from the posterior pituitary.
- Drain into cavernous sinus and IVC.
Secretion of ADH

- Most important variable is osmotic pressure of plasma and ECF.
  - Largely a function of the concentration of Na
- Osmoregulation mediated by osmoreceptors in the anteromedial hypothalamus near the supraoptic nucleus
  - Blood supply is via fenestrated capillaries, and so they are outside BBB
ADH secretion

- Osmoreceptors are sensitive to small changes in plasma osmolality.
- A decrease in osmolality of 1-2% will maximally and rapidly suppress ADH levels to allow diuresis.
- The osmostat set point in adults is a plasma osmolality of 275-295 mOsm/kg.
ADH Secretion

- ADH also released in response to non-osmotic variables
  - Decrease in blood volume or arterial pressure of more than 10-20%
    - These are mediated by neural pathways that originate in pressure sensitive receptors in the wall of the LA and projects via the vagal and glossopharyngeal nerves to the brain stem
      - Have little function in normal physiologic states
In the collecting duct blood-borne ADH binds to a V2 receptor on the baso-lateral surface of the principal tubule cell.

This stimulates adenylyl cyclase to generate cAMP and activate protein kinases.

This increases the insertion of water channels, aquaporins, into the apical surface of the cell and so increase water permeability.
• When the collecting ducts are permeable, water filters down the osmotic gradient in the medulla
  – Plasma [ADH] between 0.5 and 5 pg.ml⁻¹ accounts for the range of urine osmolalities i.e. 100 - 1250 mosmol.kg H₂O⁻¹.

• Without ADH, the collecting duct cells are impermeable to water
• ADH also acts on V1 receptors, acting as a vasopressor
  - This causes an increase in effective plasma volume, which can then downregulate ADH secretion through its action on the LA baroreceptors
• V3 receptors mediate ACTH secretion from the pituitary
• V2 receptors also act to increase Factor VIII production
Distribution and Clearance of ADH

- ADH circulates in an unbound state and equilibrates within minutes between plasma and ECF.
- Average half life is 20 minutes.
- 15-20% is filtered by glomerulus and then either destroyed or excreted.
- The rest is degraded in the liver.
ADH and Thirst: salt and water balance

- ADH function is limited, because it cannot prevent water loss in excess of that needed to excrete a certain solute load.
  - Another mechanism is needed to ensure that these, and other losses are replaced...
- THIRST
ADH and Thirst: salt and water balance

Plasma osmolality $\approx 290$ mosmoles kg $H_2O^{-1}$.

- Water lack
  - Increased osmolality
  - Osmoreceptors
    - Supraoptic PVN nuclei
    - ADH release increased
      - Lateral pre-optic area
  - Thirst increased
  - Collecting duct more permeable
  - Water retention by kidneys
  - Drinking

- Excessive water intake
  - Decreased osmolality
  - Osmoreceptors
    - Lateral pre-optic area
    - Supraoptic PVN nuclei
  - Thirst depressed
  - ADH release reduced
  - Collecting duct less permeable
  - Water loss by kidneys
Disorders of ADH secretion or action
Diabetes Insipidus
Diabetes Insipidus

- Characterized by
  - A large volume of urine (diabetes)
  - That is hypotonic, dilute and tasteless (insipid)
    - Versus the sweet urine of diabetes mellitus (honey)
Etiology

- Four fundamentally distinct defects
  - Central DI, a primary deficiency of ADH
  - Nephrogenic DI, caused by an inappropriate renal response to ADH
  - Transient DI of pregnancy, caused by vasopressinase produced by placenta
  - Primary Polydipsia, in which pathology is secondary to ingestion, rather than elimination of fluid
Central DI

- Most common
- Usually secondary to irreversible destruction of >80% ADH producing neurons
- Genetic forms caused by accumulation of poorly folded precursor proteins
<table>
<thead>
<tr>
<th>Genetic</th>
<th>Congenital</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosome 20 – dominant</td>
<td>Septo-optic dysplasia</td>
<td>Head trauma</td>
</tr>
<tr>
<td>X linked (Xq28)</td>
<td>Cleft lip and palate</td>
<td>Neoplasms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>craniopharyngioma, adenoma, lymphoma</td>
</tr>
<tr>
<td>Wolfram syndrome</td>
<td>Holoprosencephaly</td>
<td>Granulomas</td>
</tr>
<tr>
<td></td>
<td>Agenesis/hypogenisis of pit</td>
<td>Infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>meningitis, encephalitis, toxo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autoimmune</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lupus, scleroderma, wegener’s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toxins (snakes)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vascular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sheehan’s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HIE</td>
</tr>
</tbody>
</table>
Central DI

- In the OR/ICU - trauma
  - 4 year retrospective review of all ICU trauma admissions
  - DI secondary to trauma occurs as a complication 2.9% of the time
  - Overall mortality 69%
  - All patients that died developed DI within the first three days
    - Increased Mortality to 86%

Boughey, J C DI in the head injured patient, Am Surj; Jun 2004
Central DI

- Head Trauma
  - DI is often triphasic in nature
    - 1\textsuperscript{st} phase, DI, occurs within 24 hours of injury and is due to axon shock and inability to propagate action potentials to the terminals in the post pit.
    - 2\textsuperscript{nd} phase, antidiuretic phase, due to unregulated release of ADH from posterior pituitary stores as the axons die
      - This phase can occur post head injury, without 1\textsuperscript{st} and 3\textsuperscript{rd} phases
    - 3\textsuperscript{rd} phase, return of DI, occurs after all the hormone has been released
Central DI

- In the ICU/OR - Neurosurg
  - Occurs commonly in children with hypothalamic, pituitary or optic tumors
    - Craniopharyngioma is the most common non-glial tumor in the pediatric age group
      - DI develops in approx 80% of patients post-op
    - Occurs in 75% of patients following pituitary tumor resection
      - Most resolve post-op, 6% is permanent

Nephrogenic DI

- Caused by a poor response of the kidney to ADH
- Most common form is congenital
- Other forms are acquired
<table>
<thead>
<tr>
<th>Genetic</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>X linked (V2 gene)</td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td>lithium, Ampho B, rifampin,</td>
</tr>
<tr>
<td></td>
<td>cisplatin, foscarnet</td>
</tr>
<tr>
<td>Recessive (aquaporin gene)</td>
<td>Metabolic</td>
</tr>
<tr>
<td></td>
<td>hypercalcemia, hypercalcuria,</td>
</tr>
<tr>
<td></td>
<td>hypokalemia</td>
</tr>
<tr>
<td>Vascular</td>
<td>Neoplasm</td>
</tr>
<tr>
<td>sickle cell disease, ischemia</td>
<td>Neoplasm</td>
</tr>
</tbody>
</table>
Pathophysiology

• Lack of ADH, or ADH response, leads to a deficiency in urine concentration
  - 1-2% decrease in TBW, and a rise in plasma osmolality and Na
    • The latter cause a thirst response, which, if intact, stabilizes osmo’s and Na

• Polyuria further impairs concentrating ability through washout of medullary concentration gradient
Diagnosis

• Lots of stuff about fluid restriction, ADH levels, DDAVP trials, MRI’s….not useful for us
  – Useful for distinguishing between nephrogenic and central forms
    • Endocrine consult

• There is a much easier way to get what we need, and is based on simple pathophysiology
Diagnosis

• CLINICAL SUSPICION
  – Bad brain injury, neurosurg post-op
• High or increasing urine output
  – Urine Osmo usually < 300mOsm/kg
• Increasing serum Na
  – Implies free water loss in excess of sodium loss, which implicates ADH as the culprit
Treatment

- **Vasopressin**
  - 5-10 mUnits/kg/hr
  - Titrate to a level that normalizes urine output and stabilizes serum Na

- **DDAVP**
  - For chronic correction
  - More resistant than vasopressin to degradation
  - 5-20 micrograms/day by nasal spray
    - Oral and SQ forms available

- **If nephrogenic**
  - Sodium restriction and mild diuresis to encourage Na elimination
  - Gene therapy in the works….
SIADH

- Characterized by
  - Hypotonic hyponatremia
  - Impaired urinary dilution in the face of hypoosmolality
    - Urine osmolality > 100 mOsm/kg
  - In the absence of:
    - Hypovolemia
    - Hypotension
    - Adrenal insufficiency
    - Protracted emesis
SIADH

• One of the most common causes of hyponatremia in children and adults, in the hospital setting
## Etiology

<table>
<thead>
<tr>
<th>Ectopic</th>
<th>Pituitary hypersecretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasm</td>
<td>Neoplasm</td>
</tr>
<tr>
<td>carcinoma of the bronchus, ovary, bladder;</td>
<td>carcinoma of bronchus</td>
</tr>
<tr>
<td>mesothelioma; sarcoma</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Drugs</td>
</tr>
<tr>
<td>DDAVP, vasopressin, oxytocin</td>
<td>carbamazepine, nicotine, TCA, MAOI, SSRI,</td>
</tr>
<tr>
<td></td>
<td>vincristine</td>
</tr>
<tr>
<td>Head Trauma</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>Pulmonary</td>
</tr>
<tr>
<td>pneumonia, abcess of lung or brain, TB,</td>
<td>asthma, PTX, POSITIVE PRESSURE VENTILATION</td>
</tr>
<tr>
<td>encephalitis, meningitis</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>Neurologic</td>
</tr>
<tr>
<td>GBS, MS, hydrocephalus, cerebrovascular</td>
<td></td>
</tr>
<tr>
<td>occlusion or hemorrhage</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 1. Clinical Settings of Increased ADH Release in Children

<table>
<thead>
<tr>
<th>Hemodynamic Stimuli for ADH Release</th>
<th>Nonhemodynamic Stimuli for ADH Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Decreased Effective Circulation Volume)</td>
<td></td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>Central nervous system disturbances</td>
</tr>
<tr>
<td>Nephrosis</td>
<td>Meningitis, encephalitis, brain tumors,</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>head injury</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Pulmonary disease</td>
</tr>
<tr>
<td>Hypoaldosteronism</td>
<td>Pneumonia, asthma, bronchiolitis</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Cancer</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>Medications</td>
</tr>
<tr>
<td></td>
<td>Cytoxan, Vincristine, Morphine</td>
</tr>
<tr>
<td></td>
<td>Nausea, emesis, pain, stress</td>
</tr>
<tr>
<td></td>
<td>Postoperative state</td>
</tr>
</tbody>
</table>

- **Most common causes**
  - PNA
  - Bronchiolitis
  - Asthma
  - PPV
  - CNS infections
  - Head trauma
Pathophysiology

- ADH cannot significantly lower plasma Na, unless water input > output
- When this occurs, the excess ADH makes a making a dilute urine difficult
- Water accumulates in ECF and ICF compartments
- Conc of Na and other solutes decreases
- Renin and aldosterone activity decreases
  - Increases natriuresis as a response to expansion of ECF volume
- Natriuresis aggravates dilutional hyponatremia
The case against hypotonic maintenance fluids

- Many common etiologic agents cause SIADH
- Current recommendations for maintenance fluids are for hypotonic 1/2NS
- SIADH + hypotonic fluids can lead to an acute and symptomatic hyponatremia
- >50 reported cases of neurologic morbidity, including 26 deaths, resulting from hospital acquired hyponatremia in children receiving hypotonic fluids
The case against hypotonic maintenance fluids

- Children at greater risk for symptomatic hyponatremia than adults
  - Encephalopathy occurs at higher values in kids
  - Higher brain to skull ratio leaves less room for expansion
The case against hypotonic maintenance fluids

  - “isotonic saline in 5% dextrose is the safest fluid composition”
- Acute Hyponatremia Related to IV fluid administration in hospitalized children: An observational study
  - 1586 patients admitted to hospital; 40 developed hyponatremia
    - 2 with major neurologic sequelae, 1 death
    - These patients received sig. more free water than age matched controls
  - Support isotonic fluids for maintenance
Differential Diagnosis

- SIADH must be differentiated from hypervolemic, hypovolemic and other forms of euvolemic hypernatremia
- Hypervolemic hyponatremia
  - Cirrhosis, CHF
  - Always associated with edema
  - Osmotic regulation of ADH overwhelmed by a reduction in effective circulating volume, which stims ADH release
  - Secondary to hypovolemia, renin and aldosterone are increased, so there is no natriuresis
Differential Diagnosis

- Hypovolemic hyponatremia
  - Diuretic abuse, AGE, mineralocorticoid deficiency
  - Excessive loss of Na and H2O
  - Associated with signs of hypovolemia: tachycardia, hypotension
Diagnosis

• Urine osmolality >100mOsm/kg of water during hypotonicity
• Urine sodium concentration >40 mEq/L with normal dietary salt intake
• Euvolemic hyponatremia <134, Plasma Osmolality <275mOsm/L
Treatment

• Eliminate the source..

• If not:

• If hyponatremia is mild and more than 48hrs duration
  – Decrease fluid intake below insensible losses, which will slowly increase Na.
  – Watch for spontaneous remission of SIADH
    • Can occur at any time, resulting in brisk diuresis and a faster increase in serum Na than desired
Treatment

- If hyponatremia is severe (accompanied with neuro symptoms) or of less than 48 hours duration
  - Slow 3% infusion
  - Raise Na to point of cessation of symptoms
  - After above, no faster than 2 mEq/L per hour
Cerebral Salt Wasting

Harrigan, Mark *Cerebral salt wasting syndrome* Critical Care Clinics, Jan 2001
Definition

• A diagnosis of exclusion

• Requires:
  – A cerebral lesion
  – Renal Na and Cl wasting
    • Implies that above were excreted WITHOUT physiologic stimulus
      – Which means you need to have:
        – A contracted effective arterial blood volume
• So patient must not have
  – A physiologic cause for Na and Cl excretion
    • an expanded effective circulating arterial volume
  – A condition that may cause a deficiency of Na resorption
    • Aldosterone deficiency
    • diuretics
Pathophysiology

- Natriuretic Factors
- Direct Neural effects
Pathophysiology – Natriuretic Factors

- **ANP**
  - 28 amino acid polypeptide
  - Effects:
    - Natriuresis
    - Diuresis
    - Vasodilation
    - Suppression of renin and aldosterone secretion
Pathophysiology – Natriuretic Factors

- **ANP**
  - Released in response to atrial stretch
  - CNS modulates ANP secretion
    - Lesions of specific areas in hypothalamus decrease cardiac secretion of ANP in response to volume expansion
    - So, intracranial disease may lead to a disturbance in its control over ANP secretion
      - 6/8 neurosurg pts had elevated ANP levels, with a correlation between ANP level and degree of hyponatremia
      - After SAH, ADH and ANP levels elevated on days 0-2, ANP levels remained high after one week, when ADH levels declined
        - SIADH and CSW may co-exist, complicating diagnosis
Pathophysiology – Natriuretic Factors

- ANP
  - However....
  - A regression analysis of 15 patients with CSW secondary to TB mening, found plasma ANP levels accounted for only 65% of variation in plasma Na.
  - Two other factors may play a role
• BNP
  - Of cardiac ventricular origin
    • Also localized in hypothalamus
  - Secreted in response to increased pressure or stretch
  - Similar effects to ANP
  - BNP levels are elevated in patients with SAH
  - Acute intracranial disease may cause release of cardiac BNP, and hypothalamic damage may also release BNP

• Plasma Natriuretic factor
  - ?
• 40 patients with SAH, BNP levels measured
  - *Change in*, not absolute value of, BNP level independently associated with hyponatremia
  - In those in whom vasospasm developed, BNP levels increased 5.4x within 24 hours, and 11.2x within 3 days
    • BNP level independently associated with vasospasm
    • Increase in BNP did not precede vasospasm, but increased concurrently
      - May be a good marker….
    - Patients with increasing BNP levels after admission had NO CHANGE in their admit GCS after two weeks
    - Patients with no change, or decrease in BNP, had a 3 point improvement in GCS 2 weeks after admission

McGirt, MJ *CORRELATION OF SERUM BRAIN NATRIURETIC PEPTIDE WITH HYponatremia AND DELAYED ISCHEMIC NEUROLOGICAL DEFICITS AFTER SUBARACHNOID HEMORRHAGE*, Neurosurgery June 2004
Direct Neural Effects

- Generalized hyperactivity of the sympathetic nervous system occurs after SAH
  - Sustained activity leads to a decrease in plasma volume and blood volume
- Acute brain injury may lead to an interruption in sympathetic flow to kidneys
  - Increases glomerular blood flow, GFR and thus diuresis
  - Decreases renin release, and promotes natriuresis
Diagnosis

- Because those patients at risk for CSW, are also at risk for SIADH, the two must be distinguished...
<table>
<thead>
<tr>
<th>CSW</th>
<th>SI ADH</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Hypovolemia</td>
<td>*Euvolemia or hypervolemia</td>
</tr>
<tr>
<td>clinical dehydration</td>
<td></td>
</tr>
<tr>
<td>low CVP</td>
<td></td>
</tr>
<tr>
<td>Negative salt balance</td>
<td></td>
</tr>
<tr>
<td>Markedly elevated Una</td>
<td>Variable Una</td>
</tr>
<tr>
<td>Elevated K with hypoNa</td>
<td>Normal K</td>
</tr>
<tr>
<td>Serum ADH and ANP not helpful</td>
<td></td>
</tr>
</tbody>
</table>

* Likely that SI ADH and CSW, in the setting of head injury/surgery, represent two opposite ends of a spectrum:
  * pt’s probably have both exaggerated natriuresis and elevated ADH release, and which effect predominates depends on relative intensities
Treatment

• Treat underlying process
• Volume and sodium replacement
• NS, 3% NaCl, or enteral salt for restoring NaCl balance
  - Enteral salt preferable if euvolemia already restored
    • Volume expansion can lead to increased aldosterone, which can then promote more Na loss
• Restore Euvolemia
• Fludrocortisone
  - Works on renal tubule to increase Na reabsorption
  - 0.05-0.1 mg/day