The Management of Hyponatremia in Neurological Disease

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Disclosures

- Advisory Board: Sanofi/Regeneron
- No actual or potential conflicts of interest in relation to this topic/presentation.
Call Nephrology?
A dreaded problem...

Frequently encountered!
- SAH
- TBI
- CVA
- CNS infections
- Brain Tumors

Hyponatremia is present in 38-54% of cases
Definitions

Acuity
• Acute: <48 hours
• Chronic: >48 hours

Severity
• Mild: 130-134 mEq/L
• Moderate: 120-129 mEq/L
• Severe: <120 mEq/L
Symptoms

Acute
• Nausea/Vomiting
• Headache
• Seizure
• Respiratory Arrest
• Coma
• Death

Chronic
• Nausea/Vomiting
• Fatigue
• Gate instability/Falls
• Attention deficit
Sodium Regulation

- Regulated by osmoreceptors in the hypothalamus
- Normal circumstances:
  - Hyponatremia = decreased thirst and suppression of ADH
  - This results in dilute urine and normalization of sodium
Hyponatremia and the Brain

- Decreased serum osmolality
- Osmotic gradient
- Water moves into glial and neuronal cells
- Interstitial fluids migrate into the CSF → thecal sac → systemic circulation
Acute Compensation

decreases the osmotic gradient

water loss
Correction...

- Overly rapid = neurologic injury
- Water moves from the *intracellular* compartment causing rapid ↑ in electrolyte concentration & ↓ in *intracellular* volume
Osmotic Demyelination Syndrome
Take it SLOW: 4-6 mEq is all it takes!
ODS: Pathophysiology

• Most feared complication of sodium correction
  • Previously called central pontine myelinolysis

• Risk Factors:
  • Severe hyponatremia (<120 mEq/L) for more than 2-3 days
  • Alcoholism
  • Malnutrition
  • Hypokalemia
  • *Cirrhosis/Liver Transplant
ODS: Diagnosis

- Slow process
  - Delayed presentation for 2 to 6 days after rapid correction
  - More common in correction of chronic hyponatremia

<table>
<thead>
<tr>
<th>Clinical Signs</th>
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<tbody>
<tr>
<td>Psychomotor changes</td>
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<tr>
<td>Limb tremor</td>
</tr>
<tr>
<td>Psychiatric changes</td>
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<tr>
<td>Myoclonus</td>
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<tr>
<td>Catatonia</td>
</tr>
<tr>
<td>Parkinsonism</td>
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<tr>
<td>Paresis/Plegia (in and all limbs including bulbar musculature)</td>
</tr>
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</table>
ODS: Imaging

- Imaging can be normal for 4 weeks after onset

- MRI with diffuse restriction within the central pons with a trident pattern that predates T2 signal changes
ODS: Treatment

DDAVP: 2 µg IV q6h

AND/OR

D5W: 6ml/kg bolus over 2 hours
ODS: Prognosis

- Potential for neuro devastation
- Some evidence for possible improvement
  - 1/3 recover fully
  - 1/3 debilitated but independent
  - 1/3 fully dependent
- Presentation ≠ Outcome
Causes of Hyponatremia

- Polydipsia
- Low dietary solute (beer potomania)
- Diuretic Induced
- Heart Failure/Cirrhosis
- Low osmostat (pregnancy, reset)
- Exercise Induced
- SIADH
- Cerebral Salt Wasting
Cerebral Salt Wasting

Potential cause of hyponatremia in those with CNS disease—particularly subarachnoid hemorrhage.
CSW-pathophysiology?

- Unclear
  - Dysregulation of the sympathetics?
  - Natriuretic peptides
  - Adrenomedullin
- Is it real?
CSW: Clinical Features

- Moderate to Severe Hyponatremia
- Polyuria
- Occurs within 10 days of neurosurgery or event
- Dehydration
CSW: Diagnosis

- Hypovolemia
- Hyponatremia (Na <135 mEq/L)
- Low serum osms (<280 mOsm/kg)
- Elevated urine osmolality (>300 mOsm/kg)
- Elevated urinary sodium (>40 mEq/L)
- Low serum uric acid
CSW: Treatment

- Replace the sodium & water deficit
  - Infuse isotonic fluid (e.g. normal saline)
- Achieving euvolementa may not correct hyponatremia
  - Hypertonic saline (3%- 50-100ml)
SIADH

Syndrome of Inappropriate Antidiuretic Hormone
SIADH: Pathophysiology

• Supraphysiologic ADH levels ≠ osmotic changes
• Ectopic secretion of ADH
• ‘Osmostat Reset’: low osmotic threshold for ADH release

urine remains concentrated
<table>
<thead>
<tr>
<th>Type of Disorder</th>
<th>Examples</th>
</tr>
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</table>
| Brain or nervous system| **An abscess in the brain**  
Bleeding (hemorrhage) within the layers of tissue covering the brain  
**Encephalitis** (inflammation of the brain)  
**Guillain-Barré syndrome**  
Head injury  
Hypothalamus disorders, including tumors (rare)  
**Meningitis**  
**Stroke**  
**Tumors** |
| Lung                   | **Acute respiratory failure**  
**Pneumonia**  
**Tuberculosis** |
| Cancers                | **Brain cancer**  
**Lung cancer**  
**Lymphoma**  
**Pancreatic cancer**  
**Cancer of the small intestine** |
| Other                  | **Surgery**  
**Undernutrition** |

SIADH = syndrome of inappropriate secretion of antidiuretic hormone.
<table>
<thead>
<tr>
<th>Medications Associated With Syndrome of Inappropriate Antidiuretic Hormone.</th>
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<thead>
<tr>
<th><strong>Antiepileptic Medications</strong></th>
<th><strong>Psychiatric Medications</strong></th>
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<tbody>
<tr>
<td>Carbamazepine</td>
<td>Butyrophenones (haloperidol)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Monoamine oxidase inhibitors</td>
</tr>
<tr>
<td>Oxcarbazepine Sodium valproate</td>
<td>Phenothiazine (fluphenazine, chlorpromazine)</td>
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<tr>
<td></td>
<td>Risperidone</td>
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</tbody>
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<thead>
<tr>
<th><strong>Oncologic Medications</strong> Alkylating agents (cyclophosphamide) Ifosfamide</th>
<th><strong>Miscellaneous</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Bromocriptine</td>
</tr>
<tr>
<td>Platinum (cisplatin)</td>
<td>Ciprofloxacin</td>
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<tr>
<td>Vinca alkaloids (vincristine)</td>
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<tr>
<th><strong>Pain Medications</strong></th>
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<tbody>
<tr>
<td>Non-steroidal anti-inflammatory</td>
<td>Desmopressin or Vasopressin</td>
</tr>
<tr>
<td>Opiates</td>
<td>Ecstasy (methylenedioxy methamphetamine)</td>
</tr>
<tr>
<td></td>
<td>Interferon-alpha</td>
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</tbody>
</table>
SIADH: Diagnosis

- Decreased serum osmolality (<275 mOsm/kg)
- Urinary osmolality >100 mOsm/kg
- Clinical euvolemia
- Urinary sodium >40 mmol/L
- No recent diuretic use, normal thyroid, and adrenal function
Feeling Confused?
Me too...
Differentiating Cerebral Salt Wasting and Syndrome of Inappropriate Antidiuretic Hormone.

<table>
<thead>
<tr>
<th></th>
<th>Cerebral Salt Wasting</th>
<th>Syndrome of Inappropriate Antidiuretic Hormone</th>
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</thead>
<tbody>
<tr>
<td>Extracellular volume status</td>
<td>Decreased</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Unchanged to increased</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Body weight</td>
<td>Decreased</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Urine output</td>
<td>Unchanged to increased</td>
<td>Unchanged to decreased</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>Increased (relative to baseline)</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>Increased</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Serum bicarbonate</td>
<td>Increased</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Serum urate</td>
<td>Unchanged to decreased</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>&gt;100 mOsm/kg</td>
<td>&gt;100 mOsm/kg</td>
</tr>
<tr>
<td>Urine Na excretion</td>
<td>&gt;40 mmol/L</td>
<td>&gt;40 mmol/L</td>
</tr>
</tbody>
</table>
SIADH: Treatment

• Identify underlying cause
• Stop unnecessary medications
• Treatment of underlying infection
• Control pain

• Fluid restriction!!!
  • < 800 mL/d —> increase of 2 mEq/L in 24 hours
• Demeclocycline & Lithium
SIADH: Hypertonic Saline

Sodium & water excretion are regulated by independent systems → aldosterone & ADH

IV saline will not change the rate of excretion of sodium

Hypertonic saline will cause excretion of free water
Salt tablets and more...

- Increasing solute intake with:
  - Salt tablets
  - Urea
  - High-protein diet

And urine output should increase (water excretion)...

Vaptans

Activate V2 receptors in the collecting ducts to increase water excretion

Useful for both euvolemic and hypervolemic hyponatremia
Vaptans

Oral *Tolvaptan*
- Studied in cirrhosis, heart failure, and SIADH
- SALT trial: Tolvaptan vs placebo
  - Mild HN: achieved sodium > 135 within 5 days
  - Marked HN: achieved goal at 10-15 days
  - Low doses (7.5mg) are likely all that’s required to normalize sodium

IV *Conivaptan*
- Vasopressin receptor antagonist (V1, V2)
- Loading dose: 20mg over 30 minutes
- Continuous 20-40mg continued from 24-96 hours
- Good for patients in heart failure
- For TBI and neurologic injury: ↓ intracranial pressure and ↑ sodium in 4 hours
SLOW.....
Take it SLOW
The need for speed....
Hyponatremia Associated Seizure

Moderate-severe hyponatremia is also associated with seizures and even SE

Mostly generalized, but could be focal

EEG c/w metabolic encephalopathy

**Rapid correction** of Na will control seizure

5mmol/L should control seizure

- 100ml bolus of 3% over 10 minutes; repeat twice more if symptoms persist
Hyponatremic Encephalopathy

- Neurologic dysfunction 2/2 hyponatremia
- Symptoms:
  - Impaired Gait
  - Inattention
  - Headache
  - Nausea
  - Lethargy
  - Confusion/Agitation
- Risk Factors for permanent sequelae:
  - Younger age: <16, larger brain: intracranial volume
  - Premenopausal women
Hyponatremia & Cerebral Edema

- Risk Factors: stroke, infection, neoplasm, TBI
- Failure of the brain to adapt to osmotically driven forces
- Treat it as you would any cerebral edema: increase serum sodium
  - Increases in plasma sodium by 5-6mEq/L will decrease the intracranial pressure by 5 to 10 mmHg
  - 100mL bolus of 3% over 10 minutes, plus 2 additional boluses if symptoms persist
- Ongoing debate regarding the rate and method of sodium correction in the setting of cerebral edema → need more data
For Acute Severe Symptomatic:

- ↑ Na by 4-6 mEq/L can reverse impending herniation or stop seizure activity
- US: 100 mL 3% bolus over 10 minutes
  - Repeat twice more if required for symptom management
YOU DO NOT NEED A CENTRAL LINE!!!
To Review....
Duration
• Acute
• Chronic

Severity of Hyponatremia
• Mild
• Moderate
• Severe

Severity of Symptoms
• Asymptomatic
• Mild-moderate
• Severe
Initial Goals

- Make sure you collected the data
- Prevent further decline
- Prevent brain herniation
- Relieve Symptoms
- Avoid Overcorrection
Acute Hyponatremia: the first 6 hours

1. **Symptomatic**: 100 mL bolus of 3% saline infused over 10 minutes

2. **Asymptomatic**: 50 mL bolus of 3% saline over 10 minutes unless there is evidence of autocorrection (increasing output of dilute urine and/or evidence that serum sodium concentration is increasing without treatment)

3. **Goal**: ↑ increase serum sodium by 4 to 6 mEq/L over a few hours.

4. **Stop all other IVF**

5. **Seizing**: 100ml bolus of 3, if response is delayed give lorazepam 4mg IV

6. **Still symptomatic**: two additional 100 mL doses of 3% saline may be given

7. **Repeat sodium q1-2h**

8. **Monitor urine output.**
Chronic Hyponatremia: the first 6 hours

• Mild (130-134)
  • Identify cause and treat
  • Limit further intake of water

• Moderate (<130)
  • Asymptomatic patients with intracranial pathology still get treated with 3%

• Severe (<120)
  • 3% 15-30ml/hr vs 100ml boluses q6h
4-6 mEq/L in 24hrs
Proactive DDAVP Strategy

- DDAVP is started upon admission (2mcg IV q8h) and continued until sodium is close to normal
- Sodium is correct with hypertonic saline
- Oral intake is controlled/restricted

Sodium will be increased by the infused solution and not waiting on the kidney to let go of water.
Usual approach

Normal Sodium Range

Slight rise from hypertonic saline

Endogenous Overcorrection

Proactive DDAVP strategy in symptomatic hyponatremia

Normal Sodium Range

Time

Bolus of hypertonic saline and/or bicarbonate

Hypertonic Saline Infusion

DDAVP CLAMP
Thank you!
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