Hyponatremia

Manoela Braga MD
Assistant Professor of Medicine
Division of Endocrinology
McMaster University
St. Joseph’s Healthcare
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- Faculty: Dr Manoela Braga

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Outline

- Definition Hyponatremia
- Epidemiology
- Role of Vasopressin in Hyponatremia
- Cases
- Clinical Manifestations
- Diagnostic Considerations
- Treatment
Hyponatremia (Na < 135 mmol/L)

- Excess H$_2$O in relation to Na in ECF
  - Excess body H$_2$O → dilution remaining body solute
  - Depletion body solute (Na or K) relative to body H$_2$O

- Most common electrolyte disorder in clinical practice
  - 15-30% hospitalized patients
  - 4-11% ambulatory patients

- Increased mortality (even mild HypoNa)

- Mild chronic “asymptomatic” HypoNa associated gait abnormalities, falls, fractures, osteoporosis, etc...

*Am J Med 2009; 122: 679-86*
Role of AVP in Hyponatremia

- AVP secretion stimulated:
  - Increased pOsm
  - Decreased blood volume

- If pOsm falls below genetic threshold: AVP levels become undetectable → aquareesis

- SIADH: despite low pOsm: AVP release not fully suppressed

- Hypovolemia/CHF/cirrhosis: AVP release due to non-osmotic hemodynamic stimuli
Vasopressin (AVP = ADH)

AVP binds to V2 R

Collecting duct

aquaporins 2 insert into the luminal membrane

Water Reabsorption
Case 1: Mrs AM

- 85 yo, F, referred for assessment HypoNa (?AI)- significant dizziness prompted visit to ER: Na (~130)
- HPI:
  - Fatigue; chronic constipation; no N/V, appetite normal, weight stable
  - Last used steroid 3 years ago
  - Previous notes/labs- HypoNa documented since 2003
- PMHx:
  - Long standing smoldering myeloma
  - HTN
  - H/A (with recent Normal MRI)
- Medications:
  - Aspirin, Bisoprolol, Lipitor, Pantoprazole, MV
Case Mrs AM

- P/E: BP 150/75; P 76 (no orthostatic changes)
- Rest of exam unremarkable
- Investigation:
  - Cr 72; FBG 6.4
  - Na 129; k 3.7
  - AM cortisol 414; ACTH 3; TSH 7.3; FT4 17.1
  - FSH 44; LH 15.3; Prolactin 11
  - Total protein 102;
  - Hb 117; WBC 6.9; PLT 265
  - Plasma Osm 298; urine osmol 501; Na urin 100
  - Direct Na measurement: 139 mmo/L
Case 2: Mrs GG

- 68 yo, F, found comatose by family. In retrospect family recalled some forgetfulness over past few days
- Brought to ER via ambulance.
- PMHx: Osteoporosis & HTN
- Meds: Ramipril; Actonel; HCTZ (25 mg/day- started 3 weeks ago)
- P/E: Thin woman w/o focal neurological deficits; BP 140/70; P 70; W=\(~ 55Kg
Case 2: Mrs GG

- Labs: Na 117; K 2.7; Plasma Osm 250; Urin Osm 280; urinary Na 45;
- CT brain unremarkable
- Started on 3% NaCl at 50ml/h. After 2 hours Na was 122 pt has awoken; 3% saline was D/C and infusion was changed to 0.9% NaCl + K supplementation
- Next morning (about 26 h later) Na 126, patient was feeling well.
- Discharged next day with Na at 133
Approach HypoNa - Confirm True Hypo-Osmolar Hyponatremia

- Check serum osmolality to confirm truly hypo-osmolar state (< 275 mosm/Kg H$_2$O)

Differential Diagnosis
- Pseudohyponatremia (excess protein or lipid)
- Isotonic or Hypertonic Hyponatremia (Hyperglycemia/mannitol/contrast dye)

*European Journal of Endocrinology; 2014: 170, G1–G47*
Approach Hyponatremia - Symptomatic vs Asymptomatic

- Assess for serious signs/symptoms suggesting cerebral edema:
  - Seizures, coma, respiratory arrest
  - Neurogenic pulmonary edema
  - Cerebral edema with brain herniation
    - > risk children, premenopausal women

Urgent treatment with 3% saline regardless of underlying volume status, cause of hyponatremia or the time of onset!
Approach Hyponatremia -
Duration Hyponatremia

- **Acute (< 48 hours)**
  - Seizures, coma, respiratory arrest
  - Neurogenic pulmonary edema
  - Cerebral edema with brain herniation

- **Chronic (> 48 hours)**
  - N/V
  - Confusion/Personality changes
  - Gait abnormalities/Falls
  - Seizures
  - No brain herniation (unless other brain pathology)
Causes of Acute HypoNa

- Self-induced water-intoxication
  - Psychotic patients
  - Ecstasy
  - Marathon-runners

- Pos-op iatrogenic HypoNa
Brain Adaptation to Hyponatremia

- Brain cell Osmolality = Plasma Osmolality
- Early response- brain cell swelling- symptoms HypoNa
- Late response- loss of solutes – reduces brain swelling/permits survival
### “Asymptomatic” Hyponatremia

**Clinically**
- P/E:
  - vol depletion: orthostatic ↓BP, dry mucus membrane, etc..
  - vol overload: edema, ascites, pulmonary edema

*Clinical assessment of volume status has low sens and specif*

- Am J Med 1987; 83: 905
- JCEM 2008: 93: 2991

**Laboratory**
- Glucose, BUN, cr, uric acid
- Urine Osm:
  - ≤ 100 mOsm/kg: excess water intake
  - >100 mOsm/kg: inappropriately concentrated
- Spot urine [Na]
  - ≤ 30 mmol/L: low effective arterial volume
  - > 30 mmol/L: ? Diuretic use/ECF volume status
Hyponatremia

Serum Osmolality

Low

Acute or Severe Symptoms

No

Urine Osmolality

≤ 100 mOsm/Kg

Primary Polydipsia
Low Solute Intake
Beer Potomania

ECF reduced

GI (N/V, diarrhea)
Pancreatites
Burns
Excessive sweating

≤ 30 mmol/L

ECF increased

CHF
Nephrotic Synd
Renal Failure
Cirrhosis

ECF reduced

Diuretics
Primary AI
CSW

ECF Normal

SIADH
Hypothyroidism
Central AI

Normal

Hyperproteinemia (MM)
Hyperlipidemia

≥ 100 mOsm/Kg

Urine Sodium

> 30 mmol/L

Urgent 3% saline

High

Hyperglycemia
Manitol

ECF reduced
Thiazide-induced Hyponatremia

- Predominant cause diuretic-induced hyponatremia (impair distal tubule-diluting capacity without affecting urinary concentration)
- Hypov HypoNa, but urine Na high (Renal Na loss)
- Pts typically are elderly women
- Frequently occurs within few days or weeks after initiation thiazide
- Frequent recurrence after rechallenge

*J Hum Hypertens* 2002: 16:631
*Chest* 1993; 103:601
SIADH- Diagnostic Criteria

- pOsm < 275 mosm/Kg H₂O
- Inappropriate urine concentration (>100 mosm/Kg H₂O)
- Clinical euvolemic
- Urinary Na > 40 mmol/L with normal salt intake
- Exclude Hypothyroidism and AI
- No recent diuretic use

*N Engl Med 2007; 356: 2064-72*
SIADH- Causes

**Tumors**
- Small cell lung cancer
- Mesothelioma
- GI Malignancy
- Pancreatic carcinoma
- Lymphoma
- Sarcoma

**CNS Disorders**
- Tumors Subdural
- Hematoma
- Head Trauma
- Meningites

**Drugs**
- Desmopressin
- SSRI
- Tricyclic Antidepressants
- Cyclophosphamide
- “Ecstasy”

**Miscellaneous**
- HIV
- Severe nausea
- Pain
- Idiopathic

**Pulmonary Disease**
- Pneumonia
- Tuberculosis
- COPD
DD HypoNa Neurosurgical Pt Pop

- SIADH
- ACTH deficiency (Central AI)
- Injudicious use IV fluids
- Cerebral Salt Wasting (CSW)
  - Initial event: loss Na urine → vol depletion → baroreceptor-mediated AVP secretion → H2O retention → HypoNa
  - Etiology: ? Abnormal ANP; ? Abnormal BNP
  - Rx: NS to correct volume depletion
<table>
<thead>
<tr>
<th></th>
<th>SIADH</th>
<th>CSW</th>
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</thead>
<tbody>
<tr>
<td>Serum Na</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>ECFv</td>
<td>Normal</td>
<td>↓</td>
</tr>
<tr>
<td>$U_{Na}$</td>
<td>↑</td>
<td>↑ ↑</td>
</tr>
<tr>
<td>$U_{OSM}$</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Urine volume</td>
<td>N or ↓</td>
<td>↑</td>
</tr>
<tr>
<td>Serum urate</td>
<td>↓</td>
<td>N or ↓</td>
</tr>
<tr>
<td>Urine urate</td>
<td>↑</td>
<td>N or ↑</td>
</tr>
</tbody>
</table>
Rx Hyponatremia in Patients with Serious Signs/Symptoms- 3% Saline:

- Choose desired correction rate Na (e.g. 1mmol/L/h)

- \( W \) (Kg) \( \times \) desired correction rate: infuse as ml/h
  - E.g. 80 Kg \( \times \) 1 mmol/L/h = 80 ml/h infusion 3% saline

- Monitor q 1-2hs

- When to stop 3% NaCl:
  - signs/symp resolved
  - safe Na level achieved (usually \( \geq \)120mmol/L)
  - total magnitude of correction of 18 mmol/L achieved

*(Am J Med 2007; 120:S1-S21)*
Rates of Correction Chronic (>48h) Hyponatremia

- **Goals of therapy:**
  - 6 to 8 mmol/L in 24 hours
  - 12 to 14 mmol/L in 48 hours
  - 14 to 16 mmol/L in 72 hours

- **If rapid correction: risk Osmotic Demyelination**
  - > risk:
    - women (elderly women on HCTZ*), alcoholics, malnutrition, hypokalemia, burns
  - Symptoms:
    - Initial improvement → Tremor, incontinence, hyperreflexia, pathological reflexes, cranial nerve palsies, etc.

Semin Nephrol 2009; 29(3):282
J Am Soc Nephrol. 2012;23(7):1140

Pathogenesis Osmotic Demyelination

- Aggressive Rx w/ NaCl 3% outpacing brain’s ability to recapture lost organic osmolytes
- POsm > brain cell osm: water drawn out of brain cells: syndrome osmotic demyelination
Rapidly Correctable HypoNa States

- Psychogenic Polydipsia
- Thiazide-diuretic-induced
- Volume Depletion
- Desmopressin-induced
- Glucocorticoid deficiency

Desmopressin or IV water (dextrose 5%) could be used to prevent or reverse overcorrection
Rx Chronic Hyponatremia

- **Hypovolemic**
  - IV NS
  - D/C Diuretics
  - Mineralocorticoid if deficiency

- **Hypervolemic:**
  - Fluid Restriction
  - Na restriction
  - Loop diuretic
  - Treat underlying condition

*If clinical assessment equivocal:*
*trial volume expansion*
Rx SIADH

- Fluid Restriction - poorly tolerated (thirst)
- Loop Diuretics + salt tablets (to replace urin Na losses)
- Oral urea- unpleasant taste
- Enhance solute intake if poor nutrition
- D/C meds associated SIADH (e.g. SSRI)
- Treat condition associated SIADH (e.g. cancer)
- Drugs: - Demeclocycline 300-600 mg bid- can be nephrotoxic
  - Lithium- usually not indicated (side effects/toxicity)
Future Rx Options: Vasopressin Receptors Antagonists ("Vaptans")

Vaptans bind V2 R preventing activation receptor by endogenous AVP → aquareysis

NEJM 2006; 355: 2099
### Vasopressin Receptor Antagonists

<table>
<thead>
<tr>
<th></th>
<th>Tolvaptan</th>
<th>Lixivaptan</th>
<th>SR-121463</th>
<th>Conivaptan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vasopressin Receptor</strong></td>
<td>V2</td>
<td>V2</td>
<td>V2</td>
<td>V1α/V2</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Half-Life (hours)</strong></td>
<td>6-8</td>
<td>7-10</td>
<td>14-17</td>
<td>3.1-7.8</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Hepatic (CYP3A4)</td>
<td>Hepatic (CYP3A4)</td>
<td>Hepatic (CYP3A4 90%) (CYP 2D6 10%)</td>
<td>Hepatic (CYP3A4)</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>15-60 mg OD</td>
<td>50-100 mg BID</td>
<td>5-25 mg OD</td>
<td>20 mg, then 20-40 mg OD</td>
</tr>
</tbody>
</table>

Tolvaptan approved US, Europe, Canada; Conivaptan approved US
Vasopressin Receptors Antagonists- Current Role

- Management Euvolemic & Hypervolemic Hyponatremia
- Should not be used in Hypovolemic Hyponatremia
- 3% Saline: gold standard in Acute Hyponatremia
- Good efficacy/safety profile
- Side effects: thirst/ dry mouth
- Very Expensive
Take Home Message - Hyponatremia

- Check pOsm to confirm true hypo-osmolar state
- If serious signs/symptoms: urgent Rx 3% NaCl
- Determine duration development HypoNa (less or > 48h)
- Clinical assessment volume status: low sens and spec
- As a first step check urine osmolality:
  - ≤ 100 mOsm/Kg - excess water intake
  - >100 mOsm/Kg - check Urine Na
    - If Urine Na ≤ 30: low effective arterial volume
    - If Urine Na > 30: ? diuretic use/ECF status
Take Home Message - Hyponatremia

- Conservative correction goals: 6 to 8 mmol/L in 24 hours; 12 to 14 mmol/L in 48 hours; 14 to 16 mmol/L in 72 hours (if overcorrection: risk of Osmotic Demyelination)

- Rx for SIADH includes fluid restriction (first line), salt tablets, loop diuretics, demeclocycline, all of which have their limitation

- Future Rx: Vaptans - euvolemic/hypervolemic HypoNa; contraindicated Hypovolemic HypoNa

- 3% saline: still first line Rx symptomatic HypoNa