Approach to Hyponatremia
Learning Objectives

- Knowing when to apply diagnostic algorithm for hyponatremia
- Understanding better the physiological basis
  - Of some of the important tests in algorithm
  - Of some of the major groupings in algorithm
  - Of some of the important causes leading to hyponatremia
Case

- 30 yr old male
  - Known case of epilepsy (on valproate) and autism
  - Admitted for fracture of femur
  - Found to have serum Na 120 mmol/l; clinically euvoletic

- Other tests:
  - Serum urea 2.8 mmol/l, creatinine 36μmol/l
  - Serum osmolality: 248 mOsm/kg
  - Urine osmolality: 387 mOsm/kg
  - Urine sodium: 86 mmol/l
  - Serum cortisol, TFT: normal

- Diagnosis: SIADH, possibly secondary to valproate
  - But, despite significant fluid restriction and NaCl tablets
    persistent hyponatremia (120-125 mmol/l)
  - Referral for cause of hyponatremia and management
Diagnostic Algorithm for Hyponatremia

Plasma Osmolality
- Hyper
- Normal
- Hypo

Urine Osmolality
- Not Max Dilute
- Max Dilute

Volume Status (Clinical)
- Hypovolemia
- Euvolemia
- Hypervolemia

Urine Na
Hyponatremia: Preliminaries to Diagnostic Algorithm

Severely symptomatic?
- Start urgent treatment before diagnosing cause

If asymptomatic, is cause fairly obvious?
- E.g. volume depletion, cardiac failure, thiazides
- No need algorithm, start appropriate treatment

Asymptomatic, but cause not obvious
- Apply diagnostic algorithm
Diagnostic Algorithm (1)

• Hyponatremia: a state of relative water excess in relation to body sodium
• Algorithm: to ascertain which major physiological grouping of water excess patient best belongs to, before deciding underlying cause
• More than one cause possible
Diagnostic Algorithm (2)

• Generally, symptomatic hyponatremia is hypo-osmolar
  • Neurological symptoms from hypotonicity-induced cerebral oedema
• But hyponatremia also seen in hyper-osmolar and normo-osmolar states
  • Less common than hypo-osmolar group
• Therefore Step 1: serum osmolality
  • Main aim: to exclude normo- and hyper-osmolar hyponatremia
Diagnostic Algorithm for Hyponatremia

1. **Plasma Osmolality**
   - Hyper
   - Normal
   - Hypo

2. **Urine Osmolality**
   - Not Max Dilute
   - Max Dilute

3. **Volume Status (Clinical)**
   - Hypovolemia
   - Euvolemia
   - Hypervolemia

4. **Urine Na**
Hyper-osmolar Hyponatremia

- **Effective osmoles**
  - Hyperglycaemia
  - Mannitol

- **Osmoles cause hyper-osmolality and translocational hyponatremia (TBW remains same)**

- **True hyponatremia but does not cause osmotic cerebral oedema**

- **Osmolal gap > 10 with mannitol (but not glucose)**

- **Ineffective osmoles**
  - Uremia
  - Alcohol intoxication

- **Osmoles cause hyper-osmolality but not the hyponatremia (which develops because of other reasons)**

- **Hyponatremia can be true and symptomatic**

- **Osmolal gap > 10 with alcohol (but not uremia)**
Normo-osmolar Hyponatremia

• Factitious or pseudo-hyponatremia
  • Asymptomatic
  • Measured osmolality normal
  • Osmolar gap > 10 (because calculated osmolality falsely lower than measured osmolality)

• Less severe hyperglycaemia, uremia

• Use of sodium-free irrigants during TURP, laparoscopic surgery
  • Though normo-osmolar, hyponatremia can still be symptomatic for other reasons (e.g. irritant toxicity)
  • Osmolar gap > 10
Hypo-osmolar Hyponatremia: Pathophysiology

- Biggest group of hyponatremia
- Osmolar gap: normal typically
- Hypo-osmolar state can cause symptomatic cerebral oedema
- Excess water in relation to sodium in ECF = excess total body water in relation to total body sodium
  - Water intake exceeds impaired renal water excretion (majority of causes)
  - Water intake exceeds normal renal water excretion capacity (primary polydipsia)
  - Total body sodium can be decreased, normal or increased; basic problem is with water balance, not sodium balance
Hypo-osmolar Hyponatremia: Overview of Diagnostic Strategies

- Combination of establishing ADH status and volume status
- ADH status
  - Small group of causes with suppressed ADH
  - Bigger group with non-suppressed ADH
- Non-suppressed ADH group
  - Causes in this group associated with different volume status
  - Determining clinical volume status narrows down possible causes
  - Applying urine sodium to each volume group further refines diagnosis of cause
Diagnostic Algorithm for Hyponatremia

Plasma Osmolality

- Hyper
- Normal
- Hypo

Urine Osmolality

- Not Max Dilute
- Max Dilute

Volume Status (Clinical)

- Hypovolemia
- Euvolemia
- Hypervolemia

Urine Na
Hypo-osmolar Hyponatremia

• Step 2: urine osmolality
  • Main aim: to decide if state of relative water excess (i.e. hyponatremia) is with
    • ADH suppression (urine maximally dilute, i.e. < 100 mOmol/kg)
      = dilute urine group in this presentation
    OR
    • ADH secretion (urine not maximally dilute, i.e. > 100 mOsmol/kg)
      = concentrated urine group in this presentation
Hypo-osmolar Hyponatremia with Dilute Urine

- Main causes
  - Primary polydipsia
  - Poor solute intake / Beer potomania
  - Reset osmostat (with recent significant water load)
- Water retention in this group occurs through ADH-independent pathways
Poor Solute Intake

- Normal solute intake: 600 to 900 mosmol/day
- In malnourished: can be 200 to 250 mosmol/day
  - Maximum daily urine volume = urine solute per day / minimum urine osmolality
  - With maximally dilute urine, maximum urine output in malnourished can fall below 2 to 3 litres/day
  - Hyponatremia begins as fluid intake (including heavy alcohol use) exceeds this excretory capacity
Diagnostic Algorithm for Hyponatremia

1. Plasma Osmolality
   - Hyper
   - Normal
   - Hypo

2. Urine Osmolality
   - Not Max Dilute
   - Max Dilute

3. Volume Status (Clinical)
   - Hypovolemia
   - Euvolemia
   - Hypervolemia

4. Urine Na

   - Step 3
   - Step 4
Hypo-osmolar Hyponatremia with Concentrated Urine

- ADH-mediated hyponatremia
  - Exception: Advanced renal failure $\rightarrow$ ADH suppressed in this condition

- Explanation of persistent ADH secretion can be linked to body’s volume status
  - Hypovolemia and hypervolemia $\rightarrow$ ECV ↓ $\rightarrow$ ADH ↑
  - Euvolemia $\rightarrow$ unregulated ADH ↑ (i.e. by neither osmotic nor ↓ECV stimuli)

- Steps 3 and 4: assessment of volume status (clinically) and urinary sodium
  - Main aim: to ascertain underlying causes of hyponatremia in this hypo-osmolar group with concentrated urine
Clinical Volume Status

- Should be done but to be aware of its potential unreliability
- Best diagnostic signs for hypovolemia
  - Postural dizziness or increased postural pulse (Sn 60 – 98%, Sp 99%)
  - Poor skin turgour - subclavicular area (LR 3.5, but less specific in elderly)
  - Dry mouth (LR 3.1)
- Supplementary feature: serum urea to creatinine ratio > 100 (in SI units, both in mmol/L)
Clinical Volume Status (2)

- Best diagnostic signs for CCF
  - Positive hepato-jugular reflex (LR 8)
  - Displaced apex beat (LR 5.8)
  - Elevated JVP (LR 3.9)
  - S₃ gallop (LR 3.9)
- To note: serum urea to creatinine ratio can also be elevated (cardio-renal syndrome)
Urinary sodium

- An attempt to ascertain underlying cause within each volume status group
- **True hypovolemic group**
  - Urine sodium <20 mmol/l → extra-renal loss of sodium (e.g. diarrhoea); exception: vomiting with metabolic alkalosis
  - Urine sodium >20 mmol/l → renal loss of sodium (e.g. renal salt wasting, diuretics, cerebral salt-wasting)
- **Hypervolemic group**
  - Urine sodium <20 mmol/l → e.g. CCF, cirrhosis
  - Urine sodium >20 mmol/l → renal failure
- **Euvolemic group**
  - Urine sodium >20 mmol/l (with normal sodium intake)
Urinary sodium (2)

- Also affected by
  - Prior sodium intake
  - Ongoing sodium infusion
  - Ongoing diuretic effect
  - Ongoing osmotic diuresis
  - Ongoing bicarbonaturia (metabolic alkalosis)

- Interpretation of urinary sodium regarding causes of hyponatremia must consider these confounders, if present

- Generally, urine FENa is better than spot urine Na concentration to assess urine sodium status
Hypervolemic hyponatremia: Renal failure

- Main mechanisms for impaired renal water excretion
  - ↓ GFR → ↓ delivery to diluting segment
  - Rising of minimum urine osmolality to as high as 200 to 250 mOsm/kg in advanced renal failure (despite ADH suppression) because of ↑ solute excretion → ↓ urinary dilution

- Approximate urine volume in renal failure
  - Around 10% of GFR
  - E.g. advanced renal failure patient with GFR 5 ml/min (around 7l/day) cannot excrete >800 ml/day

- Water intake exceeding this urine volume capacity results in dilutional hyponatremia
Hypervolemic hyponatremia: Renal failure (2)

• With mild to moderate renal impairment (till around stage 3 CKD), there is generally sufficient urinary dilution and free water excretion to maintain normonatremia
Euvolemic hyponatremia

• Main considerations
  • SIADH and reset osmostat variant
  • Hypoadrenalism (via ADH)
  • Hypothyroidism (via ADH)
  • Thiazide use

• Generally, all these causes are associated with urine Na >20 mmol/l
  • Unless they also have poor sodium intake
Diuretic-induced Hyponatremia

- Primarily with thiazides; uncommon with loop diuretics
- Two types of presentation
  - Hypovolemia
  - Euvolemia – especially with thiazides
- Many thiazide hyponatremia cases present clinically like SIADH
  - Unlike loops, thiazides do not impair medullary osmolality (that can cause more water excretion)
  - Thus, though natriuretic, more water retention occurs with thiazides than with loops
SIADH: Main Diagnostic Criteria

- Decreased effective serum osmolality (<275 mOsmol/kg)
- Urine osmolality > 100 mOsmol/kg during serum hypotonicity
- Urine sodium > 40 mmol/L with normal salt intake
- Normal thyroid/adrenal function
- Supplementary features
  - Serum urea < 3.6 mmol/L, low normal serum creatinine
  - Serum uric acid < 0.24 mmol/L
  - Abnormal water loading test (excretion < 80% of 20 ml/kg of water load in 4 hr)
- SIADH still diagnosable with concurrent mild to moderate renal impairment
  - Such renal impairment can still dilute urine sufficiently to avoid hyponatremia
**SIADH vs Mild Hypovolemic/Low Sodium Intake**

- SIADH suspected but volume status uncertain clinically, and urinary sodium < 20 mmol/l or 20-40 mmol/l
- To note: hypovolemia or low sodium intake can co-occur in SIADH patient
- Saline infusion test (if no clinical contraindications)
- IV N/S 1 to 2 litres for 1 to 2 days with pre- and post-measurements

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<thead>
<tr>
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<th>Mild Hypovolemia</th>
<th>SIADH</th>
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<tbody>
<tr>
<td>Serum Na increase</td>
<td>≥ 5 mmol/l</td>
<td>&lt;5 mmol/l</td>
</tr>
<tr>
<td>Urine FENa increase</td>
<td>&lt; 0.5%</td>
<td>&gt; 0.5%</td>
</tr>
<tr>
<td>Urine osmolality change</td>
<td>Drops</td>
<td>Remains elevated</td>
</tr>
</tbody>
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Reset Osmostat

- Downward resetting of osmostat
- Regarded as one form of SIADH
- Seen in various conditions including
  - Normal pregnancy, quadriplegia, psychosis, TB, chronic malnutrition
- Suspected when
  - Mild hyponatremia (generally between 125 to 130 mmol/l)
  - Stable (i.e. not progressively worsening) hyponatremia despite variations in salt and water intake
- Urine osmolality may be maximally dilute or otherwise – depending on set point and water-load (plasma tonicity) status
- No treatment (including fluid restriction) needed
SIADH vs Reset Osmostat

- Water loading test
- Not to do in patients with severe hyponatremia (especially ≤ 120 mmol/l) or potential fluid overload problems
- Method
  - Supine position
  - Water load 20 ml/kg (oral or IV) over 30 min
  - Observe 4 hours
  - Monitor urine output, serum sodium, urine osmolality
- Key variable: urine output
  - Reset osmostat behaves as normal person: >80% of water load excreted
  - SIADH shows abnormal response: <80% excreted
Case Review & Summary

• Preliminary considerations
  ◦ Asymptomatic hyponatremia and cause not immediately obvious

• Diagnostic algorithm
  ◦ Step 1: Hypoosmolar hyponatremia
  ◦ Step 2: Urine concentrated (not maximally dilute) \( \rightarrow \) ADH-mediated hyponatremia
  ◦ Steps 3 and 4: Clinically euvolemic with high urine Na

• Cause
  ◦ SIADH, reasonable initial diagnosis
  ◦ However, subsequent behaviour of serum sodium with fluid restriction and salt tablets \( \rightarrow \) suggestive of reset osmostat
  ◦ Confirmed by water load test
  ◦ Off fluid restriction and NaCl tablets; serum Na two weeks later stable at 126 mmol/l and patient asymptomatic