Hyponatremia

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- Plasma Na^+ conc < 135 mM
- Due to : ↑ Arginine vasopressin (AVP)
  ↑ renal sensitivity to AVP + ↑ free water intake
- 3 groups:

1) Hypovolemic hyponatremia

- Hypovolemia → ↑ AVP → V_{1A} receptor → BP maintained
  → V_2 receptor → ↑ H_2O reabsorption
- Patient is hyperuricemic

Causes

i) Non renal

- GI Loss (vomiting, diarrhea, tube drainage)
- Sweating, burns
- Cerebral salt wasting: Hyponatremia + hypovolemia + inappropriate natriuresis + Intracranial disease like subarachnoid hemorrhage, traumatic brain injury, craniotomy, encephalitis, meningitis

ii) Renal

- Inappropriate $Na^+ - Cl^-$ loss in urine
- ↑ AVP
- ↓ aldosterone. Diagnosis confirmation by hyperkalemia + hyponatremia + hypotensive and/or hypovolemic patient with urine Na^+ much greater than 20 mM
- Salt losing nephropathies (reflux nephropathy, interstitial nephropathy, post obstructive uropathy, medullary cystic disease, recovery phase of acute tubular necrosis)
- Thiazide diuretics. Mimics SIAD
- ↑ excretion of non reabsorbable / poorly reabsorbable solute (eg: glycosuria, ketonuria, bicarbonaturia)

2) Hypervolemic hyponatremia

- ↑ in $Na^+ - Cl^-$ + even greater ↑ in total body water
- Pathophysiology similar to hypovolemic hyponatremia except that arterial filling and circulatory integrity ↓ due to CHF, cirrhosis etc
- Urine Na^+ conc typically < 10mM even after normal saline hydration

3) Euvolemic hyponatremia

Causes

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- Hypothyroidism
- 2° adrenal insufficiency

SIAD

- Most common cause
- Requires intake of water + persistent intake of serum osmolalities that are lower than threshold of water

Patterns

a) Unregulated erratic AVP secretion: In 1/3 cases
No correlation blw serum osmolality and AVP levels

b) Fail to suppress AVP secretion at lower serum osmolalities

c) "Reset osmostat" with a lower threshold osmolality

d) No detectable circulating AVP: Suggests either a gain in water reabsorption or a circulating antidiuretic substance distinct from AVP

- SIAD patients are subclinically volume expanded
- Serum uric acid <4mg/dL

TABLE 56-1 Causes of the Syndrome of Inappropriate Antidiuresis (SIAD)

MALIGNANT DISEASES	PULMONARY DISORDERS	DISORDERS OF THE CENTRAL NERVOUS SYSTEM	DRUGS	OTHER CAUSES
Carcinoma	Infections	Infection	Drugs that stimulate release of AVP or enhance its action	Hereditary (gain-of-function mutations in the vasopressin V_2 receptor)
Lung	Bacterial pneumonia	Encephalitis	Chlorpropamide	Idiopathic
Small cell	Viral pneumonia	Meningitis	SSRIs	Transient
Mesothelioma	Pulmonary abscess	Brain abscess	Tricyclic antidepressants	Endurance exercise
Oropharynx	Tuberculosis	Rocky Mountain spotted fever	Clofibrate	General anesthesia
Gastrointestinal tract	Aspergillosis	AIDS	Carbamazepine	Nausea
Stomach	Asthma	Bleeding and masses	Vincristine	Pain
Duodenum	Cystic fibrosis	Subdural hematoma	Nicotine	Stress
Pancreas	Respiratory failure associated with positive-pressure breathing	Subarachnoid hemorrhage	Narcotics	
Genitourinary tract		Cerebrovascular accident	Antipsychotic drugs	
Ureter		Brain tumors	Ifosfamide	
Bladder		Head trauma	Cyclophosphamide	
Prostate		Hydrocephalus	Nonsteroidal anti-inflammatory drugs	
Endometrium		Cavernous sinus thrombosis	MDMA ("Ecstasy", "Molly")	
Endocrine thymoma		Other	AVP analogues	
Lymphomas		Multiple sclerosis	Desmopressin	
Sarcomas		Guillain-Barré syndrome	Oxytocin	
Ewing's sarcoma		Shy-Drager syndrome	Vasopressin	
		Delirium tremens		
		Acute intermittent porphyria		

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Low solute intake and hyponatremia

- Hyponatremia occasionally in low intake of dietary solutes usually in patients whose sole nutrient is beer (beer potomania)
- In non alcoholics, hyponatremia due to nutrient restricted diets (eg: Extreme vegetarian)
- Urine osmolality usually < 100-200 mOsm/Kg with urine Na^+ < 10-20 mM
- Normal diet resumption / saline hydration will correct deficit

Clinical features

- Generalized swelling
- Primarily neurologic symptoms due to cerebral edema
- Initially, hyponatremia → Cerebral edema → ↑ interstitial pressure → Solute and ECF shunting from interstitial space into CSF and then to systemic circulation + Na^+, K^+, Cl^- efflux from brain cells
- When these volume regulatory mechanisms are overwhelmed, cerebral edema increases

- Iatrogenic sequelae when hypotonic IV fluids given to post-OP patients with ↑sed AVP

TABLE 56-2 Causes of Acute Hyponatremia
Iatrogenic
Postoperative: premenopausal women
Hypotonic fluids with cause of ↑ vasopressin
Glycine irrigation: TURP, uterine surgery
Colonoscopy preparation
Recent institution of thiazides
Polydipsia
MDMA ("Ecstasy," "Molly") ingestion
Exercise induced
Multifactorial, e.g., thiazide and polydipsia

Symptoms

- Nausea, headache, vomiting
- Severe complications of brainstem herniation, coma, death
- Normocapneic / hypecapneic respiratory failure
- Women before menopause more likely to develop encephalopathy and severe neurological sequelae
- Persistent chronic hyponatremia → Organic osmolyte efflux from brain cells → (Creatine, taurine, myoinositol etc)
  ↓ intracellular osmolality → ↑ water flow into cells
- Vomiting, nausea, confusion, seizures when serum Na^+ < 125 mM
- Chronic asymptomatic hyponatremia ↑ risk of falls and risk of fractures

Complications

- Always attempt to correct plasma Na^+ conc in Chronic hyponatremia even if symptoms absent

Osmotic demyelination syndrome

- Overly rapid correction of hyponatremia (>8-10 mM in 24 hrs / 18 mM in 48 hrs) causes hypertonic stress in astrocytes → Protein ubiquitisation, endoplasmic

reticulum stress → Apoptotic and autophagic cell death

- Classically affects pons. Extrapontine locations in cerebellum, lateral geniculate body, thalamus, putamen, cerebral cortex, subcortex

Presentation

- One to two days after over correction of hyponatremia with paraparesis, quadriparesis, dysphagia, dysarthria, diplopia, locked-in syndrome and/or LOC
- Extrapontine myelinolysis present with symptoms relevant to region affected (eg: Ataxia, mutism, parkinsonism, dystonia, catatonia)
- Slow correction can also cause ODS if risk factors present. eg: Alcoholism, malnutrition, hypokalemia, liver transplantation

Diagnostic approach

- Detailed drug history, assess volume status
- Consider all causes of ↑ AVP (volume status, drugs, nausea and/or pain)
- Radiological imaging for pulmonary / CNS cause. CT scan if small cell Ca suspected (smoking)

Lab investigations

- Serum osmolality to exclude pseudohyponatremia (hyponatremia + ↑ plasma tonicity)

Hyponatremia = serum osmolality < 275 mOsm/kg

- ↑ BUN/Creatinine? → Renal cause

  Hyperkalemia? → Adrenal insufficiency / hypoaldosteronism

  Hyperuricemia? → Volume depletion

  Hypouricemia? → SIAD type physiology

- Plasma Na^+ conc ↓ by ~1.6-2.4 mM for every 100mg/dL increase in glucose
- Check thyroid, adrenal and pituitary function as they cause euvolemic hyponatremia

- 1° adrenal failure → Hypovolemic hyponatremia. Co syntropin stimulation test to assess 1° adrenal insufficiency
- Urine Na^+ < 20-30 mM? → Hypovolemic hyponatremia, beer potomania

  Urine Na^+ > 30mM? → SIAD
- Gold standard for hypovolemic hyponatremia → Plasma Na^+ correction when hydrated with NS
- Urine osmolality <100mOsm/Kg → Polydipsia

  Urine osmolality >400 mOsm/Kg → AVP excess

  Urine osmolality <100-200 mOsm/kg → Beer potomania

Treatment @tribaincol

- 3 major considerations:
  i) Presence and/or severity determine urgency and goals
  ii) Chronic hyponatremia causes ODS if plasma Na^+ corrected by >8-10mM in <24 hrs and/or by >18mM within <48 hrs
  iii) Response to hypertonic saline/isotonic saline/AVP antagonist highly unpredictable, needs constant monitoring

Euvolemic hyponatremia

- Due to hypothyroidism/SIAD/2° adrenal failure
- Respond to treatment of underlying cause
- If SIAD +ve, frusemide 20mg BD + tab NaCl works initially but can cause hypokalemia and/or renal dysfunction. Demeclocycline if furosemide + NaCl does not work but can cause natriuresis and/or direct renal toxicity
- Palatable doses of oral urea given in SIAD comparable in efficacy to AVP antagonists (Vaptans)

AVP antagonists (Vaptans) @tribaincol

- Highly effective in SIAD, hypervolemic hyponatremia due to HF/cirrhosis
- Tolvaptan is the only oral V_2 antagonist.
- Conivaptan only available IV vaptan is a mixed V_{1A}/V_2 antagonist, causes moderate risk of hypotension
- Vaptan therapy started in a hospital setting with >2L/d fluid intake and plasma Na^+ monitoring
- Tolvaptan in significant and persistent SIAD not responding to water restriction and/or furosemide and NaCl
- Tolvaptan therapy only for <1-2 months

Hypovolemic hyponatremia

- IV hydration with isotonic normal saline → ↓AVP, brisk diuresis
- Reduce rate of correction if hyponatremia for >48 hrs

Hypervolemic hyponatremia

- Due to CHF
- Treat cardiomyopathy (eg: ACE inhibitors)

Beer potomania @tribaincol

- Respond rapidly to IV saline + normal diet
- High risk of ODS

- H_2O restriction is the cornerstone of therapy. Calculated with:

$$\text{Urine-to-plasma electrolyte ratio} = \frac{\text{Urinary } Na^+ + K^+}{\text{Plasma } Na^+}$$

>1 = <500mL/day
~ 1 = 500-700mL/day
<1 = <1L/day

- If hypokalemia, K^+ replacement helps ↑ plasma Na^+ conc
- If fluid restriction, K^+ replacement, ↑ solute intake fails, pharmacological therapy started

Acute symptomatic hyponatremia

- Hypertonic 3% saline (513mM) to ↑ plasma Na^+ by 1-2 mM/h to a total of 4-6mM. This alleviates acute symptoms.
- Chronic hyponatremia treatment started afterwards
- Bolus 100mL better than infusion
- If infusion, estimate required rate by: @tribaincol

$$Na^+ \text{ deficit} = 0.6 \times \text{Body weight} \times (\text{target plasma conc} - \text{Starting plasma conc})$$

Hypertonic saline has an Na^+-Cl^- of 513mM. Calculate rate using it
Plasma Na^+ monitoring every 2-4 hrs during treatment

- Oxygen and ventilatory support is critical in acute hyponatremia as pulmonary edema, hypercapneic respiratory failure can occur. Pulmonary edema treated with loop diuretics
- AVP antagonists have no role in treating acute hyponatremia

Chronic hyponatremia @tribaincol

- Rate of correction: <6-8 mM in first 24 hrs, <6mM each subsequent 24 hrs
- Lower target rates in hypokalemia, alcoholics
- Overcorrection when AVP rapidly normalizes (eg: following treatment of patients with chronic hypovolemic hyponatremia with IV saline or glucocorticoid replacement in patients with hypopituitarism / 2° adrenal failure)
- Risk ↑ if <2L/day fluid intake
- If over correction, hyponatremia reintroduced by AVP agonist desmopressin acetate (DDAVP) and/or free water administration