Polyuria and Diabetes Insipidus

Polyuria:

- Definition: Urine output > 30cc/kg/day or > 3 liters/day.
- Patients usually become symptomatic at 4-6 l/day.
- Differential diagnosis: in outpatient setting patients will nearly always have either uncontrolled diabetes mellitus and glucosuria, diabetes insipidus, or psychogenic polydipsia; but must also consider salt-wasting nephropathy, hypercalcemia, hypokalemia or medications. Distinguish between water diuresis (DI) and solute diuresis (glucose, diuretics, resolving acute renal failure).

Diabetes Insipidus:

Definition: excess urinary loss of solute free water.

- Uncommon: approx. 3/100,000
- Patients present with marked polyuria and polydipsia with high serum osmolarity (>295) and inappropriately LOW urine osmolarity (<300).
- Results from either insufficient or absent ADH or renal insensitivity to ADH (antidiuretic hormone or arginine vasopressin).
- Patient is unable to conserve water if deprived access to fluids.
- Thought to be under-recognized.

Normal Physiology:

- Recall actions of ADH. There are two known receptors Vasopressin 1 (V1) has vasoconstrictor and prostaglandin activity, and Vasopressin 2 (V2) has antidiuretic, vasodilator, and coagulation factor mediator (causes release of factor VIIIc and vonWillebrand factor from endothelial cells) activities.
- Normal serum osmolarity is maintained in narrow range: 285-295 mOsm or mMol/kg,. Urine osmolarity ranges from 100-1200 mOsm/kg, depending on the need to conserve or excrete free water.
- When dehydrated, rising serum osmolarity (>280) is sensed by osmoreceptors of the anterior pituitary triggering release of ADH by the posterior pituitary.
- ADH binds to V2 receptors of renal collecting duct causing increased permeability to water (water channels called aquaporins float free in the cytosol and are signaled by ADH to embed in the membrane) and thus
more free water is absorbed by the kidneys. Concentrating ability is maximal when serum osm is >295 mOsm/kg.

- Thirst is triggered (osmoreceptors of thirst center of the hypothalamus) when serum osmolarity exceeds 290 mOsm/kg.

- Thus, in setting of water deprivation or dehydration, the body compensates by concentrating urine and by stimulating the urge to drink.

- Note that for maximal renal concentrating ability, the renal medullary gradient must be intact.

- Other stimulants of ADH secretion include hypovolemia (>10% loss of blood vol), hypoglycemia, nausea, some drugs (nicotine, carbamazepine, clofibrate).

- DIABETES INSIPIDUS occurs when this compensating mechanism is disrupted. The person excretes large volume of dilute urine and must take in large volume of dilute solution to maintain normal fluid and electrolyte balance.

**Classification of Diabetes Insipidus:**

- Neurogenic or Central – absent or insufficient ADH Can be 1° (familial autosomal dominant, or idiopathic thought to be autoimmune), or 2° usually due to some intracranial event (trauma, surgery, tumor).

- Nephrogenic or Peripheral – renal insensitivity to ADH. Can be 1° (familial, X-linked recessive defect in V2 receptor or very rare in aquaporin), or 2° most often to Lithium (impairs cAMP in collecting duct and thus inhibits water reabsorption), but also from infiltration (inflammation or infection, e.g. sarcoid, Sjogrens, TB), or from hypercalcemia.

- Excessive destruction of ADH by vasopressinases.

- Polydipsia – either dipsogenic (abnormal thirst center) or psychogenic.

- Disorder occurs with range of severity (termed partial central or partial nephrogenic). Mild forms do exist in which patients can partially respond to fluid restriction by increasing resorption of water at the level of the proximal tubule or by making use of baseline partial permeability of the collecting duct in the absence of ADH. Elderly persons and persons with renal failure have a mild renal insensitivity to ADH, but this is often asymptomatic.

Neurogenic: **Idiopathic; Acquired:** neoplastic (craniopharyngioma, lymphoma, meningioma, met. Carcinoma, other brain tumor), head trauma, neurosurgery, Ischemia (shock, s/p arrest, Sheehan’s syndrome, aneurysms, sickle cell crisis); granulomatous (sarcoid, histiocytosis), Infectious (TB, encephalitis, meningitis), autoimmune, familial.

Nephrogenic: **Familial, Acquired:** Drug induced (lithium, demeclocycline, methoxyflurane), metabolic (hypokalemia, hypercalciuria usually with hypercalcemia), renal disease (polycystic kidneys, obstructive uropathy, chronic pyelonephritis, sickle cell nephropathy, sarcoïd, chronic renal failure, multiple myeloma, Sjogren’s disease, analgesic nephropathy); **Idiopathic.**

**Clinical Manifestations:**

- Thirst, often craving cold water, nocturia, polyuria (volumes can be 3-18 l/day).
Dilute urine, specific gravity < 1.005, osmolarity < 200.

Serum osmolarity nears 300 mOsm/kg, but may be normal with ready access to fluids.

If fluids withheld, serum osmolarity rises dramatically! Leads to hypertonic encephalopathy. Mental status change is due to fluid shifts at cellular level in the brain. Patients present with marked dehydration, MS changes and neurologic symptoms.

Absence of nocturia or low serum osmolarity should raise suspicion of psychogenic polydipsia.

Time course and setting of presentation often provides clue to etiology:

**Neurogenic** usually presents abruptly after insult but can be insidious with tumor or idiopathic (familial presents age 1-2, idiopathic usually occurs 3:2 in males: females with mean age presentation 16 yrs). In 5-10% of pts with DI after CNS insult, DI usually follows 3 predictable phases: initial polyuric/hypotonic phase followed by some improvement as damaged pituitary cells leak residual ADH (days 6-11), then permanent DI due to lack of ADH.

**Nephrogenic** is usually more gradual; unless familial - congenital absence of V2 receptors or aquaporins causes presentation in the neonatal period (fever, vomiting, MS changes, hypernatremia) leading to CNS damage.

**Pregnancy** often unmasks mild DI. Placenta produces vasopressinases, threshold for thirst and ADH are altered, renal sensitivity to ADH is altered. Gestational DI improves post-partum.

**Differential Diagnosis:**

- Psychogenic Polydipsia – mimics DI (actually is a form of DI). Water intake can reach 20 l/day and the medullary gradient is depleted causing diminished renal concentrating ability. Can be behavioral (most often middle-aged women), psychiatric + drugs, or can be from lesion in thirst center "dipsogenic polydipsia" (e.g. sarcoid).

- Medications causing dry mouth stimulate water intake (antipsychotics, anticholinergics).

- Salt-wasting nephropathy.

In the inpatient setting polyuria may be caused by the above, but also watch for:

- Uncontrolled diabetes mellitus.

- Post-obstructive diuresis.

- High-protein feeding – urea load leads to solute diuresis.

- Post-operative diuresis due to intraoperative hydration.

- Medications (mannitol, steroids)

- s/p radiocontrast load

- s/p resuscitation – diereses of large volume of fluids given.
**Diagnosis:**

History is often suggestive but usually need to confirm DI unless hypertonicity makes water deprivation dangerous.

**Water Deprivation ADH Stimulation Test:**

Confirms DI and distinguishes between neurogenic, nephrogenic or psychogenic polydipsia.

**Method:**

- Controlled environment!!!
- Induce state of mild dehydration. Try to get serum osm >300, because at this point further ADH will not be effective in normal situation. (may need to give 3% NaCl to get osm > 300)
- Measure UOP, urine sp gr, serum Na, serum osm hourly
- Document adequate dehydration (5% wt loss, serum osm >295), steady state ( < 30 mOsm change in urine osm for 2 consecutive measurement).
  
  (note if urine osm reaches >600-800 at this point, then the ADH and renal response are adequate/normal, no need to proceed).
- Measure ADH level. (special collection method, on ice)
- Give ADH, 5 units SQ.
- Continue to measure urine and serum osmolarity and UOP hourly.

Interpret by evaluating the relation of the urine and serum osmolarities and ADH in response to dehydration and ADH administration. Absolute numbers are less important than the relative changes. Test is inconclusive in 10% of cases, in which case plotting ADH level/ osm measurement on nomogram can be helpful.

DI is confirmed if urine osm stays low despite increased serum osm.

**Response to ADH:**

- Central – urine osm will increase by at least 50% and UOP, Na, and serum osm will decrease.
- Partial central or partial nephrogenic - urine osm increases by 10-50%.
- Nephrogenic - no change in urine osm.
- Psychogenic polydipsia - urine osm increases but by < 9%
- Absolute ADH level after water deprivation - <1.0 in neurogenic; high in nephrogenic
- Abort test if patient develops symptoms of vascular compromise or hyperosmolarity. Testing and interpretation may need to be modified in pregnancy.
• Future possibilities for diagnosis: measurement of aquaporin level in urine (expensive, not widely available)

Treatment:

Treatment is indicated if symptoms of polyuria and polydipsia are debilitating and due to risks if access to fluids is in question. Patients can tolerate symptoms for years so disorder is often overlooked.

Goal: correct pre-existing deficits and reduce ongoing losses

• Central: Try to determine cause, may need CNS imaging. Treat with DDAVP 10mcg qhs or BID– nasal vasopressin, a synthetic analog of ADH without the pressor or uterine effects. Nasal form is best tolerated, easiest to administer, and most consistently absorbed. Duration of effect varies from 8-20 hours. Cost $2/dose. Undertreat to avoid volume overload and hyponatremia. Need to watch serum sodium very closely! Can supplement with short acting lysine vasopressin.

Side effects of DDAVP (usu. mild) include headache, nausea, nasal congestion, rhinitis, flushing, abdominal cramping. Can cause angina and blood pressure.

• Partial DI: may respond to drugs which stimulate ADH and potentiate its action: chlorpropamide, but hypoglycemia may be limiting factor. ADH is also stimulated by carbamazepine and clofibrate.

• Nephrogenic: Some meds can decrease polydipsia by decreasing total body salt so isotonic absorption of water by the proximal tubule is increased. Usually use thiazides, amiloride, or both. Patients need to adhere to low salt diet. Need to watch fluid status closely. Although it seems counter-intuitive to give diuretics, this works essentially by inducing a state of mild dehydration and thus causing maximal compensation by other renal mechanisms.

• Adjunctive treatment is NSAIDs (via prostaglandin effects to increase response to ADH)

• Treatment of choice for Lithium induced DI is amiloride (mechanism not clear), but usually not effective if pt has been on Lithium for a long time.

• For patients who also have disrupted thirst mechanism, treatment is extremely difficult.

Once treatment is started, very important to avoid unplanned treatment withdrawal. Unplanned withdrawal usually occurs from:

• 1. pt noncompliance (pt education VERY important)
• 2. Medical emergency (pts should wear medic alert tag specifying diabetes INSIPIDUS)
• 3. Iatrogenic inadvertence (pt made NPO for some reason… record needs to be flagged that pt is undergoing tx for DI)

References:


