Water, Water, Everywhere, and Not ENOUGH to Drink: A Case of Isolated Diabetes Insipidus then Evolving Pituitary Dysfunction

Leigh Pughe, RN, MS, CPNP
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Conflicts of Interest

- The speaker has no conflicts of interest to disclose

Objectives

- Endocrine evaluation of polyuria and polydipsia
- Endocrine treatment of diabetes insipidus
- Discussion of endocrine concerns with Langerhans Cell Histiocytosis (LCH)
Patient: DI
Presented to PCP
- 10 years 6 months
- Chief Complaint at PCP: "feeling tired and drinking a lot of water"
- HPI
  - 2 months of polydipsia, drinking over 1 gallon of water per day
  - Urinating often
  - When he does not have access to water, he feels excessively thirsty
  - No diet change, abdominal pain, vomiting, diarrhea
  - No recent illnesses
  - No history of head trauma
- Past Medical and Surgical History:
  - R elbow fracture repair at age 4 years
- Social:
  - Lives with parents and siblings, does well in school, 5th grade
- Medications: None

Review of Systems
- Constitutional: negative; no recent weight loss
- HEENT: negative
- Endocrine: positive for polyuria, polydipsia. Negative for cold intolerance, heat intolerance, polyphagia
- Genitourinary: positive for urinary frequency. Negative for dysuria, hematuria, penile swelling, scrotal swelling, enuresis
- Musculoskeletal: negative for joint swelling
- Hematological: negative for abnormal bleeding or bruising

Physical Exam
- Weight: 109 pounds
- Constitutional: well-appearing, no acute distress
- Cardiovascular: regular rate and rhythm, S1 S2 normal, no murmur
- Palp/CV: lungs clear to auscultation
- Abdominal: nontender, nondistended without masses or hepatosplenomegaly
- Skin: intact without rashes or lesions
Patient DI: Labs

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (135–145 mEq/L)</td>
<td>146 (H)</td>
</tr>
<tr>
<td>Urine Specific Gravity (1.001–1.035)</td>
<td>1.003</td>
</tr>
<tr>
<td>A1c</td>
<td>4.9%</td>
</tr>
<tr>
<td>Osmolality, Urine (300–1300 mOsm/kg)</td>
<td>65 (L)</td>
</tr>
<tr>
<td>Serum Osmolality (275–300 mOsm/kg)</td>
<td>316 (H)</td>
</tr>
<tr>
<td>Calcium (8.5–10.5)</td>
<td>10.5</td>
</tr>
</tbody>
</table>

Referred to Nephrology for concern for diabetes insipidus...

Patient DI: Nephrology Consultation

- HPI as before
- Physical Exam: Pulse 116 bpm, Weight 110 pounds; unremarkable physical exam
- Plan:
  - Fast for 11–12 hours and then obtain first morning urine for osmolality
  - Renal Ultrasound
Patient DI: Labs

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Color</td>
<td>Yellow</td>
</tr>
<tr>
<td>Appearance, Urine</td>
<td>Clear</td>
</tr>
<tr>
<td>Urine Specific Gravity</td>
<td>1.003</td>
</tr>
<tr>
<td>(1.001 - 1.035)</td>
<td></td>
</tr>
<tr>
<td>Urine pH</td>
<td>6.5</td>
</tr>
<tr>
<td>(5.0 - 8.0)</td>
<td></td>
</tr>
<tr>
<td>Protein, Urine Random</td>
<td>Negative</td>
</tr>
<tr>
<td>Ketones, Urine</td>
<td>Negative</td>
</tr>
<tr>
<td>Blood Glucose</td>
<td>Negative</td>
</tr>
<tr>
<td>Urine Nitrites</td>
<td>Negative</td>
</tr>
<tr>
<td>Urine Bilirubin</td>
<td>Negative</td>
</tr>
<tr>
<td>Urine Leukocytes</td>
<td>Negative</td>
</tr>
<tr>
<td>Osmolality, Urine</td>
<td>67.8 (L)</td>
</tr>
<tr>
<td>(300 - 1300) mOsm/kg</td>
<td></td>
</tr>
<tr>
<td>OSMOLALITY</td>
<td>302 (H)</td>
</tr>
<tr>
<td>(275 - 295) mOsm/kg</td>
<td></td>
</tr>
<tr>
<td>Serum Sodium</td>
<td>143</td>
</tr>
</tbody>
</table>

Reflected to endocrinology...


di

di

di

Patient DI: Endocrine Consultation

- HPI as before
  - For past 3-5 months, parent noticed increase in water intake and urine output. He has to go to the bathroom overnight and drinks a lot of water.
  - Parent reports symptoms started abruptly and have mostly remained stable.
  - No neurological symptoms such as headache, loss of balance. No nausea, abdominal pain, vomiting, diarrhea, or constipation.
  - Sometimes has dry lips.
  - Family History obtained – noncontributory (hypertension and osteoporosis in grandparents).
Evaluation of Polyuria & Polydipsia

Polyuria and polydipsia
- Quantification of urine output and fluid intake
- Can range in symptoms
  - Babies: unexplained recurrent fevers, vomiting, excessive crying, irritability, excessively wet diapers
  - Younger children: primary enuresis
  - Older children: nocturia, high urine output

Differential Diagnoses of polyuria/polydipsia
- Central diabetes insipidus (AVP secretion and/or synthesis)
- Nephrogenic diabetes insipidus (AVP resistance)
  - Most common in children
- Primary polydipsia (psychogenic polydipsia or defective thirst mechanism)
- Osmotic diuresis – diabetes mellitus, urea diuresis, sodium diuresis

Evaluation of Polyuria & Polydipsia (continued)

Initial Labs
- Serum & Urine osmolality
- BMP: Na, K, Glucose, Ca, BUN
- Urinalysis: Glucose, Specific Gravity
- If serum osmolality < 300 mOs/m/kg + urine osmolality <300 mOs/m/kg
  - Diabetes Insipidus
- If serum osmolality > 300 mOs/m/kg + polyuria
  - Water Deprivation Test
- If serum osmolality <270 mOs/m/kg OR urine osmolality >50
  - Diabetes Insipidus unlikely

- If serum osmolality > 300 mOs/m/kg + urine osmolality <300 mOs/m/kg
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- If serum osmolality > 300 mOs/m/kg + polyuria
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Water Deprivation Test for Diabetes Insipidus

- Suspicion of Diabetes Insipidus
  - Urine Osm < 300 mOsm/kg Serum Osm > 300 mOsm/kg
- Fluid Restrict Patient
- Measure every hour:
  - Weight, BP, Pulse
  - Urine volume, creatinine, specific gravity, sodium
  - Serum osmolality, sodium (BUN at baseline & end)
- Vasopressin level measured at baseline & end
- Discontinue test when one of the following occur:
  - If weight loss > 5% of starting weight
  - If plasma sodium > 145 mEq/l
  - If plasma osmolality is higher than 300 mosm/kg
  - If urine osmolality increases to normal
- Allow to drink, administer Pitressin 1 unit/m2 SQ

Evaluation of Polyuria & Polydipsia: Water Deprivation Test

Central Diabetes Insipidus: A Review

- Characterized by polyuria due to deficiency in arginine vasopressin (AVP)
  - AVP works on the kidney to increase urine osmolality
- Water balance: thirst, AVP, kidney function
Diabetes Insipidus:
Central vs Nephrogenic

<table>
<thead>
<tr>
<th>Condition</th>
<th>Urine Osm - after fluid deprivation</th>
<th>Urine Osm - after Pitressin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Diabetes Insipidus</td>
<td>&lt;300 mosm/kg</td>
<td>&gt;750 mosm/kg</td>
</tr>
<tr>
<td>Nephrogenic Diabetes Insipidus</td>
<td>&lt;300 mosm/kg</td>
<td>&lt;300 mosm/kg</td>
</tr>
<tr>
<td>Primary Polydipsia</td>
<td>&gt;750 mosm/kg</td>
<td></td>
</tr>
<tr>
<td>Partial DI/undetermined</td>
<td>300 – 750 mosm/kg</td>
<td>&lt;750 mosm/kg</td>
</tr>
</tbody>
</table>

Central Diabetes Insipidus: A Review
Arginine Vasopressin Secretion & Thirst

- Arginine Vasopressin Secretion & Thirst

Central Diabetes Insipidus: Evaluation

- Brain MRI
  - Possible findings
    - Pituitary stalk thickening (>3 mm)
    - Posterior pituitary hypointensity ("bright spot")
    - Mass
  - If widened pituitary stalk
    - MRI repeat every 3-6 months in first 3 years
    - Biopsy of pituitary stalk if > 6.5 mm
- Skeletal survey
- Tumor markers
Central Diabetes Insipidus: Management

- Free water access
- DDAVP (Desmopressin)
  - Preparations
    - PO = better absorption, fewer complications, better compliance
      - DDAVP 0.1 and 0.2 mg/daily or 0.5 mg/daily with food
    - Intranasal (drop or solution)
      - 100 mcg/mL: 5-30 mcg/24h divided daily or BID
    - Parenteral
      - 0.1 and 0.5 mg/IV divided BID
  - Monitoring
    - Patient should have diuresis before next dose
    - Electrolyte monitoring
    - Hypotonicity, nausea, vomiting, headache, seizure
  - (Low sodium diet)

Central Diabetes Insipidus: Differential Diagnosis

- Acquired:
  - Craniopharyngioma, Germinoma
  - Langerhans Cell Histiocytosis (LCH), Lymphocytic hypophysitis
  - Sarcoidosis
  - Infectious (meningitis, encephalitis) or Local inflammation/Autoimmunity
  - Autoimmune/vascular disease
  - Trauma to base of brain
  - Tuberculosis
  - Drugs
  - Idiopathic
- Congenital:
  - Malformation of the brain (septo-optic dysplasia; holoprosencephaly)
  - Familial autosomal dominant central diabetes insipidus
  - Familial autosomal recessive (Wolfram Syndrome)

Langerhans Cell Histiocytosis (LCH)

- Excess histiocyte cells (specifically Langerhans cells) which infiltrate many areas of the body including CNS, skin, bone, lung, liver, spleen
- Affects about 1:200,000 children
- Single system vs Multisystem
- Imaging: about 50-70% of patients have pituitary stalk thickening (not always at presentation)
- Extra-cranial lesions
  - Skeletal (skull survey) - 80%
  - Dermatological - 50%
  - Lung (chest x-ray)
  - Liver
    - Pharynx - 25%
- Diagnosis: biopsy of the affected tissue
- Treatment: surgery, steroids, NSAI/NS, low dose radiation, chemio, BMT/transplant

Langerhans Cell Histiocytosis (LCH): Endocrine Considerations

- Most frequent manifestation of LCH: Central Diabetes Insipidus
  - Up to 50% of patients
- 2nd most frequent manifestation of LCH: Growth hormone deficiency
  - Around 10% of patients
- Delayed puberty - rare
- Panhypopituitarism - rare

Case of DI: Evaluation

- Water Deprivation Test
  - Physical Exam:
    - Positive for dry, chapped lips
    - HR 111 bpm
    - Weight 103 lbs
  - Vasopressin 1 unit/m² was administered subcutaneously with subsequent labs (obtained at 30-minute intervals up to 2 hours after vasopressin administration)

<table>
<thead>
<tr>
<th></th>
<th>Pre-DDAVP</th>
<th>1 hour Post-DDAVP</th>
<th>2 hour Post-DDAVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Na (mEq/l)</td>
<td>150 (H)</td>
<td>148</td>
<td>146</td>
</tr>
<tr>
<td>Serum Osm (mOsm/kg)</td>
<td>324 (H)</td>
<td>307 (H)</td>
<td>289</td>
</tr>
<tr>
<td>Urine SG</td>
<td>&lt;1.005</td>
<td>1.010</td>
<td>1.013</td>
</tr>
<tr>
<td>Urine Osm</td>
<td>86 (L)</td>
<td>213 (L)</td>
<td>457</td>
</tr>
<tr>
<td>Arginine Vasopressin (ng/mL)</td>
<td>&lt;1.0 (L)</td>
<td>1.0 (L)</td>
<td>3.2 (L)</td>
</tr>
</tbody>
</table>

Back to the patient…
Case of DI: Evaluation

- Increasing urine osmolality and downtrending sodium and serum osmolality which confirmed:

**Central Diabetes Insipidus**

- MRI brain with and without contrast
  - Thickened hypothalamic-pituitary stalk and small (2-3mm) questionable enhancement in the anterior pituitary
- Pediatric Hematology/Oncology consult
- Skeletal Survey
  - No focal osseous lesions
- Pediatric Ophthalmology consult
  - No gross visual field deficits or papilledema on exam
- Neurosurgery Consult
  - No neurosurgical intervention at this time
- X-ray Chest: Clear
- Additional labs
  - Tumor markers (hCG, AFP) – negative
  - LDH, lactic acid – normal

Case of DI: Management

- Admitted for evaluation and monitoring
  - No intravenous fluids (due to intact thirst mechanism)
  - Strict IDAs with goal UOP 1-2 cc/kg/h
  - Received DDAVP 0.1 mg prior to bed and then required another dose 12 hours later
- DI was discharged on DDAVP 0.1 mg PO BID
Case of DI: Continued monitoring

- Serial Brain MRI
  - 3 months: Thickening and increased enhancement of the pituitary stalk, with the midportion measuring up to 4mm in thickness. Slightly increased from size in prior study. Pituitary gland is normal in signal and homogeneous in enhancement without focal lesion. The infundibulum is deviated slightly to the left. The differential diagnosis includes inflammatory etiologies such as hypophysitis or granulomatous disease. Metastatic tumor is less likely.
  - 9 months: The pituitary stalk is enlarged, up to 5mm in thickness. It is more prominent when compared to prior studies. There is no normal T1 hypointense signal in the expected location of the posterior pituitary, unchanged from previous studies.
- Heme/Onc and Tumor board follow up
- Endocrine follow up
- Rheumatology evaluation

Case of DI: Endocrine Evaluation

### Growth

<table>
<thead>
<tr>
<th></th>
<th>September 2017</th>
<th>May 2018</th>
<th>May 2018</th>
<th>August 2018</th>
<th>January 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin-like Growth Factor 1 (IGF-1) Mass Spec</td>
<td>123 - 410 ng/mL</td>
<td>159</td>
<td>85 (L)</td>
<td>122 (L)</td>
<td>99 (L)</td>
</tr>
</tbody>
</table>

Case of DI: Endocrine Evaluation

### Thyroid

<table>
<thead>
<tr>
<th></th>
<th>September 2017</th>
<th>May 2018</th>
<th>May 2018</th>
<th>May 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid Stimulating Hormone</td>
<td>0.40 - 4.60 uU/mL</td>
<td>2.05</td>
<td>2.15</td>
<td>3.30</td>
</tr>
<tr>
<td>Free Thyroxine F4</td>
<td>0.8 - 1.7 ng/dL</td>
<td>1.50</td>
<td>0.83</td>
<td>0.79 (L)</td>
</tr>
<tr>
<td>Thyroxine (T4)</td>
<td>4.50 - 12.00 ug/dL</td>
<td>8.83</td>
<td>4.89 (L)</td>
<td></td>
</tr>
</tbody>
</table>

Started on levothyroxine in May 2018
Case of DI: Endocrine Evaluation → Puberty

<table>
<thead>
<tr>
<th></th>
<th>May 2018</th>
<th>May 2018</th>
<th>August 2018</th>
<th>January 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone, Total, Mass Spec.</td>
<td>14</td>
<td>6</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>&lt;=260 ng/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone Free</td>
<td>1.5</td>
<td>1.1</td>
<td>0.7</td>
<td>1.0</td>
</tr>
<tr>
<td>0.7 - 10.0 pg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Case of DI: Endocrine Evaluation → Cortisol

<table>
<thead>
<tr>
<th></th>
<th>September 2017</th>
<th>May 2018</th>
<th>August 2018</th>
<th>January 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>19.0</td>
<td>17.0</td>
<td>12.2</td>
<td>12.0</td>
</tr>
<tr>
<td>5.0 - 25.0 ug/dL</td>
<td></td>
<td>21.3</td>
<td>(stimulated)</td>
<td></td>
</tr>
</tbody>
</table>

Case of DI: Patient updates

- Ongoing endocrine evaluation every 3 months for pituitary function
- Tumor markers remain negative – germinoma less likely, still possibility. LCH remains possible diagnosis
- LP negative for tumor markers
- Has had 2nd and 3rd opinions, all agree
  - Absent bright spot is seen with central diabetes insipidus, does not lead to diagnosis
  - Observation alone vs empiric therapy with steroids with presumptive diagnosis of early LCH
  - 3 month MRIs for 1st 2 years then less frequently
Resources


Thank you!