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

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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 5 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

Patient DI (continued)

- 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

Patient DI (continued)

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

Patient DI : Labs

Sodium (135-145 mEq/L)	146 (H)
Urine Specific Gravity (1.001-1.035)	1.003
A1c	4.9%
Osmolality, Urine (300 - 1300) mOsm/kg	65 (L)
Serum Osmolality (275 - 295) mOsm/kg	316 (H)
Calcium (8.5 – 10.5)	10.5

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

Urine Color	Yellow
Appearance, Urine	Clear
Urine Specific Gravity (1.001-1.035)	1.003
Urine PH (5.0-8.0)	6.5
Protein Urine Random (Negative)	Negative
Urine Glucose	Negative
Ketone, Urine	Negative
Blood Urine	Negative
Urine Nitrites	Negative
Urine Bilirubin	Negative
Urine Leukocytes	Negative
Osmolality, Urine (300 - 1300) mOsm/kg	67 (L)
OSMOLALITY (275 - 295) mOsm/kg	302 (H)
Serum Sodium	143

Referred to endocrinology…

Patient DI : Endocrine Consultation

- HPI as before
  - For past 2-3 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

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 mOsm/kg + urine osmolality <300 mOsm/kg
  → Diabetes Insipidus
- If serum osmolality < 300 mOsm/kg + polyuria
  → Water Deprivation Test
- If serum osmolality <270 mOsm/kg OR urine osmolality >60
  → Diabetes Insipidus unlikely

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, osmolality, 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

Water Deprivation Test

ENDOCRINE FUNCTION TEST — Patient Name

DIAGNOSIS: Suspected Diabetes Insipidus

TEST: Water Deprivation

Present Health: _____ Good _____ Fair _____ Poor

Diet for previous two days (attach diet history), is several tobacco, ethanol:

Initial period of fast_____hr

Initial body weight_____kg Recent Medications:

Thirst sensation assessed:_____

Hr	Hour	Interval Minutes	Body weight	Vital signs	Serum Na	Serum OSM	Serum BUN	Plasma VP	Urine Na	Urine OSM	Urine TLC	Urine Vol/Hr
		-30		Place IV/ start lock								
		0	X	X	X	X	X	X	X	X	X	X
		60	X	X	X	X				X	X	X
		120	X	X	X	X			X	X	X	X
		180	X	X	X	X				X	X	X
		240	X	X	X	X		X	X	X	X	X
		300	X	X	X	X				X	X	X
		360	X	X	X	X			X	X	X	X
		420	X	X	X	X				X	X	X
		480	X	X	X	X	X	X	X	X	X	X

*If patient has D, last VP sample at last time point before VP administration (see below)

AT ANY TIME DURING TEST:
If serum sem >300 (Na>145), urine osm <800, continue test unless vital signs disclose hypovolemia
If urine osm >1000, or <800 and stable (<50 mosm change for 2 time points), stop test = NORMAL
If serum osm <300 and urine osm<800=DIABETES INSIPIDUS. Give Pitressin, 1U/m2 SQ and measure

TIME AFTER PITRESSIN ADMINISTRATION:

		30		X						X	X	X
		60		X					X	X	X	X

COMMENTS:

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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

	Urine Osm - after fluid deprivation	Urine Osm – after Pitressin
Central Diabetes Insipidus	<300 mosm/kg	>750 mosm/kg
Nephrogenic Diabetes Insipidus	<300 mosm/kg	<300 mosm/kg
Primary Polydipsia	>750 mosm/kg	
Partial DI/ undetermined	300 – 750 mosm/kg	<750 mosm/kg

Central Diabetes Insipidus: A Review Arginine Vasopressin Secretion & Thirst

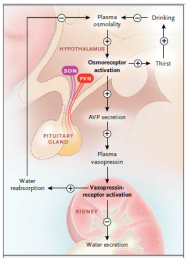

Figure 1. Feedback Loop Governing Regulation of Plasma Osmolality through Control of Arginine Vasopressin Secretion and Thirst.

An increase in plasma osmolality activates hypothalamic osmoreceptors to stimulate vasopressin secretion by the posterior pituitary gland. The resulting increase in the level of plasma vasopressin leads to an increase in renal water reabsorption and a decrease in water excretion. Increased water reabsorption reduces plasma osmolality. Osmosensing in the hypothalamus also stimulates thirst and drinking to help restore plasma osmolality. AVP denotes arginine vasopressin, PVN paraventricular nucleus, and SON supraoptic nucleus.

Knepper MA, et al. Molecular Physiology of Water Balance. N Eng J Med. 2015. 372;1349.

Central Diabetes Insipidus: Evaluation

- Brain MRI
  - Possible findings
    - Pituitary stalk thickening (>3 mm)
    - Posterior pituitary hyperintensity ("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: Start at 0.05 mg/dose PO daily or BID; titrate to effect
    - Intranasal (spray or solution)
      - Spray: 100mcg/mL: 10 mcg/spray → 5-30 mcg/24h divided daily or BID (>12y: 10-40 mcg/24h divided daily or TID)
    - Parenteral
      - >12 y: 2-4 mcg/24h divided BID
  - Monitoring
    - Patient should have diuresis before next dose
    - Electrolyte monitoring
    - Hyponatremia – nausea, vomiting, headache, seizure
- (Low salt 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
  - Skeleton (skeletal survey) – 80%
  - Dermatological – 33%
  - Lung (chest x-ray)
  - Liver
  - Pituitary – 25%
- Diagnosis: biopsy of the affected tissue
- Treatment: surgery, steroids, NSAIDS, low dose radiation, chemo, BMT/transplant

Haupt R, Minkov M, Astigarraga I, et al. Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. *Pediatr Blood Cancer.* 2012;60(2):175–184. doi: 10.1002/pbc.24367

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

Back to the patient…

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)

	Pre-DDAVP	1 hour Post-DDAVP	2 hour Post-DDAVP
Serum Na (mEq/L)	150 (H)	148	146
Serum Osm (mOsm/kg)	324 (H)	307 (H)	289
Urine SG	<1.005	1.010	1.013
Urine Osm	86 (L)	212(L)	457
Arginine Vasopressin (pg/mL) (1.0 – 13.3)	<1.0 (L)		

Case of DI: Evaluation

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

Central Diabetes Insipidus

Case of DI: Evaluation

- 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
- Xray Chest: Clear
- Additional labs
  - Tumor markers (hCG, AFP) -- negative
  - LDH, uric acid -- normal

Case of DI: Management

- Admitted for evaluation and monitoring
  - No intravenous fluids (due to intact thirst mechanism)
  - Strict I/Os 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 homogenous 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 hyperintense 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

	September 2017	May 2018	May 2018	August 2018	January 2018
Insulin-like Growth Factor 1 (IGF-1) Mass Spec 123 - 497 ng/mL	159	85 (L)	122 (L)	99 (L)	88 (L)

Case of DI: Endocrine Evaluation → Thyroid

	September 2017	May 2018	May 2018
Thyroid Stimulating Hormone 0.40 - 4.60 uU/mL	2.05	2.15	3.30
Free Thyroxine Ft4 0.8 - 1.7 ng/dL	1.50	0.83	0.79 (L)
Thyroxine (T4) (5.00 - 12.00) ug/dL	8.83		4.49 (L)

Started on levothyroxine in May 2018

Case of DI: Endocrine Evaluation → Puberty

	May 2018	May 2018	August 2018	January 2019
Testosterone, Total, Mass Spec. <=260 ng/dL	14	8	5	9
Testosterone Free 0.7 - 52.0 pg/mL	1.5	1.1	0.7	1.0

Case of DI: Endocrine Evaluation → Cortisol

	September 2017	May 2018	August 2018	January 2019
Cortisol 5.0 - 25.0 ug/dL	19.0	17.0 (baseline) 21.3 (stimulated)	12.2	12.0

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

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Thank you!