A 7-year-old Girl with Intermittent Vomiting, Abdominal Pain, and Weight Loss

Robert Listernick, MD

This 7-year-old girl was admitted to the hospital for evaluation of intermittent vomiting, abdominal pain, and weight loss. At a well-child visit 3 months earlier, she was noted to have fallen off her growth curve in height and weight. Her height dropped from 25th percentile to less than the fifth percentile and her weight dropped from the 75th percentile to the 10th percentile. At that time, she had normal serum chemistries, complete blood count, celiac antibody testing, and thyroid function tests. IGF-1 and IGF-binding protein-3 were both at the lower limits of normal. She had started to gain weight in the last 2 months with the addition of some caloric shakes. Shortly after returning from a camping trip, she began having intermittent abdominal pain associated with brief episodes of nonbilious, nonbloody vomiting.

On review of systems, she denied any headaches, vision changes, diarrhea, respiratory symptoms, fever, arthritis, or rash. Past medical history was unremarkable. She was taking no medications. Family history was unremarkable.

On physical examination, she was tearful and complaining of abdominal pain. Weight and height were both just below the fifth percentile. She was afebrile, pulse 90, respiratory rate 16, and blood pressure 93/65. She had dry, cracked lips. Her sclerae were white; her throat was clear; neck was supple; lungs were clear. S1 and S2 were normal without murmurs, rubs, or gallops. Abdomen was soft and nontender without organomegaly. Her hands and feet were cool to the touch with normal capillary refill and perfusion. Skin and neurologic examination were normal.

On admission, her CBC, erythrocyte sedimentation rate, C-reactive protein, urinalysis, electrolytes, liver function tests, amylase, and lipase were normal.

Dr. Liem, MD, moderator:

Red flags?

Robert Listernick, MD, general academic pediatrician: She clearly has lost weight and is malnourished. More importantly, her growth velocity has plummeted. Without giving away the answer, I think there is one diagnosis that should stand out.

Dr. Liem: Initially, the focus was on the possibility of either poor nutritional intake or inflammatory bowel disease.

Dr. Listernick: I can understand considering the possibility of inflammatory bowel disease, but she has a normal CBC, serum albumin, and inflammatory markers. I have a hard time believing she has Crohn’s disease severe enough to cause growth deceleration without her having an abnormality in some or all of these tests.

Dr. Liem: I agree with that line of reasoning, despite the significant abdominal pain.

Sonia Sterrett, MD, pediatric resident: During the initial history, her mother had mentioned that she seemed to urinate more than her siblings. She actually keeps a bottle of water by her bedside at night and wakes up multiple times to drink and urinate. On a recent 3-hour trip, the family had to stop the car multiple times so she could urinate. It was difficult to pinpoint the beginning of these symptoms, but they have probably occurred for as long as 7 months.

Dr. Listernick: This is a perfect example of a case in which you’ll get the right answers if you know what questions to ask.
Dr. Liem: She seems to be suffering from polyuria and polydipsia. What questions should you ask if you suspect the presence of diabetes insipidus (DI)?

Reema Habiby, MD, pediatric endocrinologist: Of course, one would look at a urinalysis to make sure that you’re not dealing with diabetes mellitus. As Dr. Sterrett did, questions about nocturia, nighttime drinking, and urinating on long car rides are important. In addition, I like to inquire about the preferred fluid to drink. Invariably, the answer is water and not higher solute-containing fluids such as soda or fruit juice.

Robert Tanz, MD, general academic pediatrician: We see a number of children who have psychogenic polydipsia. They have similar symptoms, except that they don’t drink excessively after they go to sleep.

Dr. Habiby: Agreed. My first step would be to look at a first morning void and measure the urine osmolality, which should be high in healthy children.

Dr. Liem: On the day of admission, her serum electrolytes sodium were 144 mEq/L; potassium 4.2 mEq/L; chloride 107 mEq/L; bicarbonate 26 mEq/L; BUN 16 mg/dL; creatinine 0.4 mg/dL; glucose 45 mg/dL. Urinalysis was normal save for 1+ ketones with a specific gravity of 1.003. The next morning, her urine osmolality was 89 mosm/L, quite low.

Dr. Habiby: She’s clinically dehydrated, yet she has a very low urine specific gravity and bland urine. That virtually clinches the diagnosis of DI.

Dr. Liem: Is this information sufficient to establish the diagnosis of DI?

Dr. Habiby: I would proceed with a water deprivation test. An important point is that one should never perform a water deprivation test at home. If the patient is drinking a lot at night, pediatricians should never tell the parents to withhold water. Patients who truly have DI can become dehydrated very rapidly and develop severe hypernatremia if not carefully monitored.

Dr. Liem: If you are able to test a first morning void, what level of osmolality would be sufficient to eliminate the diagnosis of DI?

Dr. Habiby: Somewhere around 600 mosm/L.

Dr. Liem: After 8 hours of water deprivation test, her urine was still very dilute, but her serum sodium didn’t change.

Dr. Habiby: This does not firmly establish the diagnosis of DI. Most likely, she has partial DI; you could probably fast her for another 8 hours and not conclusively prove she has DI. She probably makes just enough antidiuretic hormone to maintain normal serum sodium.

Dr. Liem: Does she have central or nephrogenic DI?

Dr. Habiby: At the end of a water deprivation test, we always administer pitressin to see if the patient can concentrate her urine. She responded to the pitressin, proving that she has central DI.

Dr. Liem: I should also point out that she had a very elevated serum prolactin noted early in the evaluation.

Dr. Habiby: Elevated prolactin doesn’t necessarily imply the presence of a prolactinoma. Often, a mass effect in the hypothalamic region or pituitary stalk causes loss of active inhibition of prolactin secretion. The most common intracranial lesions that present with DI in this fashion are germinomas and Langerhans cell histiocytosis (LCH).

Joanna Weinstein, MD, pediatric neuro-oncologist: It’s important to point out that both germinomas and LCH can present with DI long before there is any radiologic evidence of the tumor. Children who present with central DI who initially have normal MRI scans need to be followed longitudinally for years to monitor for their appearance.

Dr. Liem: Can we see the neuro-imaging?

Delilah Burrowes, MD, pediatric neuroradiologist: There is abnormal thickening and deviation of infundibular stalk of the pituitary gland. There was mild focal enhancement of the hypothalamus. In addition, there was an absent pituitary bright spot. The remainder of the brain was normal. My first thought was that this looked most like an inflammatory granulomatous process, such as sarcoidosis. Certainly it also could have been neoplastic.

Dr. Liem: What do you mean by an “absent pituitary bright spot”?

Dr. Burrowes: Normally on the T1-weighted images, the anterior pituitary is homogeneously dark, like the gray matter, while the posterior pituitary is “bright.” This bright spot is absent in some patients who have congenital hypopituitarism and in most who have acquired DI from any of the stated causes.

Dr. Liem: How did you proceed?

Jason Fangusaro, MD, pediatric neuro-oncologist: We thought that there was a subtle fullness to the
infundibular mass and that this was most likely a brain tumor. First, we looked for evidence of LCH outside the CNS. She had a normal skeletal survey and computerized tomography scan of the chest and abdomen.

**Dr. Liem**: What is LCH?

**Dr. Fangusaro**: LCH is a clonal proliferation of pathologic cells in a single organ or in multiple organs. There are myriad presentations, ranging from isolated skin or bone disease (eosinophilic granuloma) to diabetes insipidus to severe life-threatening multisystem disease. LCH involvement of the pituitary stalk might not be evident radiographically on initial presentation but become apparent only months to years later.

**Dr. Habiby**: It’s not uncommon for LCH patients to present with combined DI and growth hormone deficiency.

**Dr. Fangusaro**: The other tumor that we considered was a germ cell tumor. Germ cell tumors are not necessarily confined to the testicles or ovaries and may arise anywhere in the body. We believe they are derived from remnants of embryonic cells left behind as they migrated down the primitive notochord to their final location in the gonads. In the central nervous system, they tend to occur in the midline in the pineal gland and the hypothalamic area.

**Dr. Liem**: How can you decide the cause of this girl’s endocrinopathy?

**Dr. Fangusaro**: It’s extremely problematic. Some children with germ cell tumors have elevated levels of alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (beta-HCG) in the serum and the cerebrospinal fluid (CSF). We can also look at the cytology of the CSF for abnormal cells. CSF beta-HCG is more sensitive than serum beta-HCG for detection of germ cell tumors.

It becomes even more complicated. There are pure germinomas and mixed malignant germ cell tumors. Non-germinal mixed germ cell tumors are more aggressive and more difficult to treat, requiring aggressive therapy. Germinomas are very treatable. Elevated AFP in the context of a brain tumor is thought to be diagnostic of non-germinal mixed germ cell tumor. Elevations of beta-HCG are not as clear. She had an elevated beta-HCG, eliminating the possibility of LCH.

**Art DiPatri, MD, pediatric neurosurgeon**: We would like to get tissue for pathology, if possible. However, there are significant risks to biopsying the suprasellar region. For children who have large suprasel-
lar masses, biopsy is not generally a problem. This child has a very small lesion that would be quite difficult to biopsy safely. Even if we biopsy the lesion and decide that it’s a pure germinoma, we might miss the malignant area of a “mixed” tumor.

**Dr. Fangusaro:** So we’re sure she has a tumor in the CNS germ cell tumor category with a mildly elevated beta-HCG. This combination — isolated pituitary lesion, prolonged DI and mildly elevated beta-HCG — almost always indicates a pure germinoma. However, we couldn’t definitely exclude the possibility of a more aggressive tumor.

**Dr. Liem:** How did you decide how to treat her?

**Dr. Fangusaro:** We had a frank discussion with the family and outlined all the thorny issues in diagnosis and treatment. Ultimately, it was decided to give her more aggressive therapy with a combination of chemotherapy and radiotherapy used for non-germinal mixed germ cell tumors. The chemotherapy consists of combinations of carboplatin and etoposide, alternating with ifosfamide and etoposide. We will tailor her radiotherapy based on her response to therapy, including radiographic imaging changes and tumor markers. If she has an excellent response, it’s another indication that it is pure germinoma. We would consider whole ventricular field radiotherapy with a boost to the tumor bed rather than craniospinal radiation, which is often used for non-germinal mixed germ cell tumor. Recent studies have shown that with similar treatment schedules, we achieved 85% to 90% 3-year event-free overall survival in both pure germinoma and non-germinal mixed germ cell tumors.

**Dr. Liem:** Thank you, everybody.

**Key Learning Points**

1. Children who have diabetes insipidus prefer to drink water over other higher solute fluids.
2. Physicians should never perform water deprivation tests at home. If the patient is drinking a lot at night, pediatricians should never tell parents to withhold water for fear of precipitating a hypernatremic dehydration crisis.
3. The most common intracranial lesions to present with diabetes insipidus are germinomas and Langerhans cell histiocytosis (LCH).
4. Germ cell tumors of the central nervous system tend to occur in the midline in the pineal gland and the hypothalamic area.