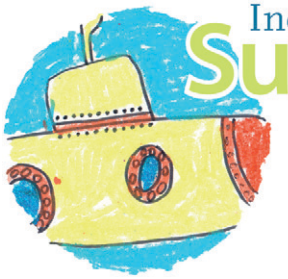

Index of Suspicion

1 An 11-year-old Girl with Depression and Electrolyte Disturbance

Raymen Rammy Assaf, MD, MPH, MIA,* Maria Levine, MD,† Clement Cheung, MD, PhD,‡ Benita Tamrazi, MD,§ Jennifer A. Cotter, MD,¶** Michael Bryant, MD, MBA,†† Erin N. Kiehna, MD‡‡

*Department of Pediatrics, †Division of Psychiatry, Department of Pediatrics, ‡Division of Endocrinology, Department of Pediatrics, ¶Department of Pathology and Laboratory Medicine, and ††Division of Hospital Medicine, Department of Pediatrics, Children's Hospital Los Angeles, Los Angeles, CA §Department of Radiology, **Department of Pathology, and ‡‡Division of Neurosurgery, Department of Surgery, Children's Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA

EDITOR'S NOTE

On June 3, 2017, 27-year-old Alex Honnold climbed the 2,900-foot rock face of El Capitan in Yosemite National Park, alone and with neither rope nor safety net. The story is shown in the 2018 documentary film *Free Solo* and described in the 2018 book *The Impossible Climb* by Mark Synnott.

Many reading this issue of *Pediatrics in Review* have moved to new levels of responsibility this summer and might feel like they are free-soloing too.

Honnold did not do his free-solo climb on a whim. He prepared meticulously. He worked with colleagues and practiced moves for years, with ropes, on the same route that he would one day conquer on his own, unsupported. Just as with pediatric training, expertise comes with training, time, and practice.

But, what did Honnold do during the afternoon of June 3, 2017, following what the *New York Times* called "one of the great athletic feats of any kind, ever"? He worked out to strengthen his grip for future climbs. In the same way, we who care for children keep working out. We keep honing our skills. We meticulously study possible "routes" as we consider cases and differential diagnoses and management plans. After each patient care success, we keep "working out" for the next challenge.

Even so, may you use this month's *Index of Suspicion* cases to "strengthen your grip" so you can be effectively prepared to work through steep diagnostic challenges as you reach new heights of pediatric practice.

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

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PRESENTATION

An 11-year-old girl with a 2-year history of major depressive disorder presents to the emergency department with 10 days of anorexia, irritability, and depressed mood. She was first diagnosed as having depression 2 years ago during a 2-month-long hospitalization that mandated a psychiatric hold for physical

aggression and suicidal ideation with concurrent anorexia requiring nasogastric feeding. Aripiprazole 1 mg daily was prescribed to target symptoms of agitation. After discharge from her first hospitalization, the patient was followed monthly by a psychiatrist and weekly by a psychotherapist, with discontinuation of pharmacotherapy 4 months later given improvement in labile mood.

Then, 11 months after that point, she was noted to clinically deteriorate, with development of severe apathy, irritability, oppositionality, and anorexia despite the absence of identifiable stressors. She was admitted again, this time for 2 weeks, for treatment of depression, oral aversion, and anorexia. Aripiprazole therapy was briefly reinitiated, but the patient was thought to have medication-induced dystonia (fist-clenching) and syndrome of inappropriate antidiuretic hormone, with a serum sodium level of 118 mEq/L (118 mmol/L). Sodium values returned to normal levels after water restriction, oral sodium supplementation, and discontinuation of aripiprazole. Concurrent diffuse headaches were evaluated with a contrast computed tomographic scan of the head, which did not demonstrate any structural abnormality or calcification. On discharge, mood and behavior were improved on fluoxetine 10 mg nightly. However, after approximately 6 weeks, the patient's depression, irritability, aggression, and oral intake worsen, and she is seen in our emergency department for these symptoms, meeting the criteria for inpatient psychiatric hospitalization.

The patient measures 51.6 in (131 cm) in height (less than the third percentile, z score $= -2$) and weighs 65 lb (29.3 kg) (eighth percentile, z score $= -1.39$), with a BMI of 18.85 (67th percentile, z score $= 0.5$), growth velocity of 1.0 in (2.5 cm) per year, and midparental height of 61.5 in (156.25 cm). Although she demonstrated a poor growth trajectory, the patient had limited follow-up with her primary pediatrician, and no previous endocrinologic evaluation had been completed. Vital signs on presentation are within normal limits, and the physical examination reveals a Tanner stage I prepubertal female (pubic hair I, breasts I) with no neurologic deficit. She is seen by a psychiatry consultant in the emergency department and is diagnosed as having major depressive disorder recurrent episode with atypical features, including increased sleep.

She is admitted to the hospital for close observation and is started on mirtazipine to target depression and poor oral intake. She develops asymptomatic hypoglycemia (glucose level of 52 mg/dL [2.9 mmol/L]) and hyponatremia (sodium level of 125 mEq/L [125 mmol/L]). Her morning cortisol level is low (<1 μg/dL [<27.6 nmol/L]), with an inappropriately normal corticotropin level (9 pg/mL [2 pmol/L]) and a subsequent failed corticotropin stimulation test, with a peak cortisol level of 2.7 μg/dL (74.5 nmol/L). Additional endocrine evaluation reveals a low free thyroxine level (0.68 ng/dL [8.75 pmol/L]), with an inappropriately normal thyrotropin level (1.41 mIU/L), a low insulinlike growth factor I level (45 ng/mL [5.9 nmol/L], −3.4 SD), and prepubertal gonadotropin and estradiol levels. Further evaluation reveals the etiology of her condition.

DISCUSSION

Gadolinium-enhanced magnetic resonance imaging (MRI) of the brain is performed, demonstrating a cystic mass in the sella measuring 1.4 × 1.4 × 2.1 cm with suprasellar extension, displacing the optic chiasm superiorly (Fig, top row). Cyst contents are hyperintense on T1-weighted MRI and predominantly hypointense on T2-weighted MRI, with hemosiderin staining on the gradient recalled echo sequence suggestive of previous hemorrhage. Given the new findings on MRI, an underlying sellar mass supports the reason for the endocrinologic disturbances recently discovered in this patient. A differential diagnosis includes a hemorrhagic Rathke cleft cyst (RCC), predominantly cystic craniopharyngioma, hemorrhagic macroadenoma, and a germ cell tumor.

The Disorder

Central endocrinopathy is frequently associated with sellar masses, and given the patient's indolent symptoms and MRI findings, an RCC was suspected. Both RCC and adamantinomatous craniopharyngioma (ACP) originate from ectopic remnants of the Rathke pouch formed during embryonic development of the pituitary gland and have similar clinical manifestations. (1) An ACP is more likely to have calcifications on imaging, which were absent in this case. (2) On pathologic examination, an ACP typically contains squamous epithelium, whereas an RCC characteristically contains well-differentiated columnar epithelium and cilia, although the 2 conditions have been reported to coexist given their common embryologic origin. (3) In this patient, serum and cerebrospinal fluid α-fetoprotein and β–human chorionic gonadotropin test results were both negative, making germ cell tumor unlikely.

Most RCCs are asymptomatic, with the incidence ranging from 3% to 22% in adult autopsy studies. (4) Although only 10% of RCCs are found in patients younger than 16 years, these are usually symptomatic, prompting brain imaging. (5) When RCC enlargement causes acute or subacute symptoms, it commonly manifests over a period of weeks to years with headache (70%–85% of patients), visual impairment (33%), and endocrine dysfunction (66%), with diabetes insipidus, precocious puberty, and growth delay the most frequently encountered endocrinopathies. (5)

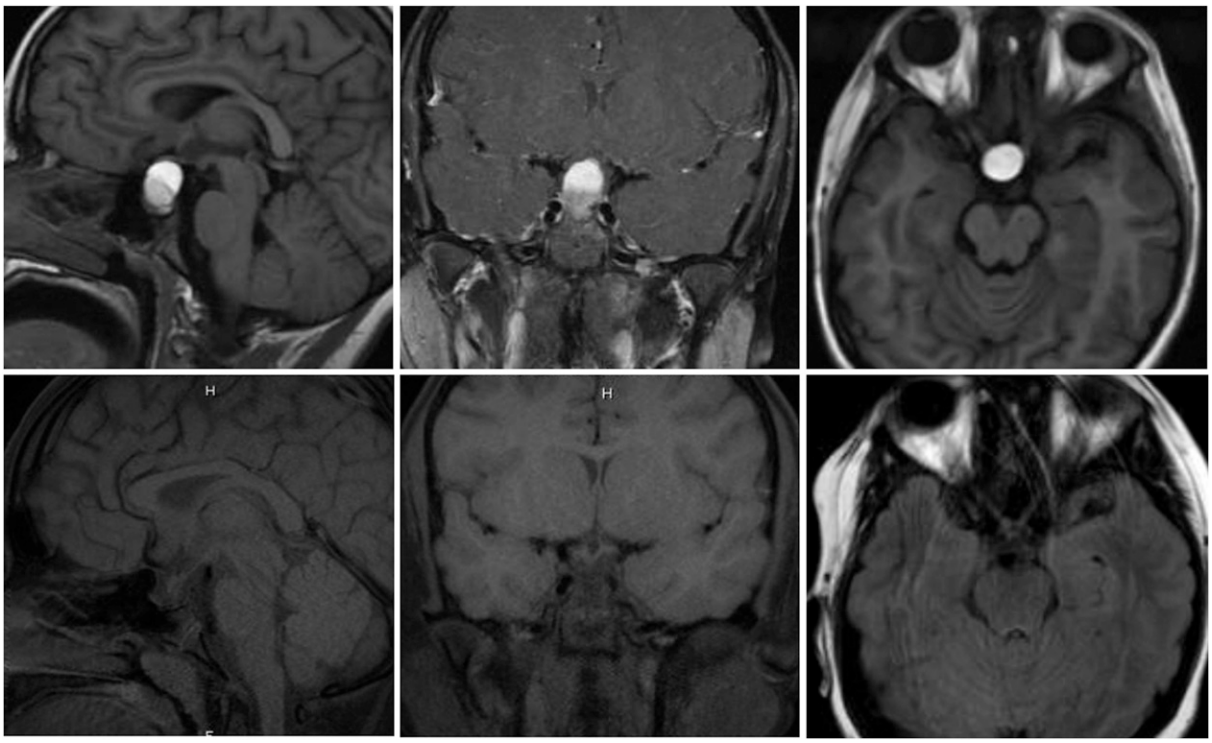

Figure. Comparison of preoperative T1-weighted magnetic resonance images (MRIs) (upper row) and MRI with dedicated images of the sella 18 months after resection via the transsphenoidal approach (bottom row). The hyperintense cystic lesion originally measured 1.4 × 1.4 × 2.1 cm, with displacement of the optic chiasm superiorly. No residual cyst is evident in the postoperative images.

Intracystic hemorrhage or inflammation secondary to cyst contents is possible and may lead to a more severe acute presentation. (5)

Diagnosis and Treatment

Clues to an underlying central endocrinopathy early in our patient's hospital admission included headache and vomiting in an 11-year-old prepubertal female patient whose height measured less than the third percentile for age, with concurrent and persistent hyponatremia (sodium level of 125–130 mEq/L (125–130 mmol/L). These findings together ultimately prompted an evaluation of a morning cortisol level and further endocrinologic evaluation, which revealed evidence of relatively low corticotropin, thyrotropin, and growth hormone levels. Bone age was found to be concordant with chronological age. An ophthalmologic examination revealed bitemporal superior quadrantanopsia and normal visual acuity, consistent with inferior chiasmal compression.

Although behavioral disturbance and executive dysfunction are well-documented consequences of hypopituitarism and in particular hypocortisolism, an association specifically between RCC and psychiatric manifestation is less described in the literature. (6) To begin with, the true incidence of pituitary cysts in childhood is not known but is thought to be uncommon, with asymptotic lesions incidentally found in 4 of 341children (1.2%) younger than 15 years in a 10-year single-center retrospective review of brain MRIs. (7) According to national mental health surveillance data for 2005 to 2011 from the Centers for Disease Control and Prevention (CDC), the prevalence of depression in children aged 3 to 17 years was reported to be 2.1%. (8) A delay in the diagnosis in our case may be attributed to the slow growth of RCC and the indolent course of additional somatic symptoms other than headache as well as limited access to primary pediatric and endocrine specialty care during the 2 years between the diagnoses of mood disorder and pituitary mass. Panhypopituitarism at the time of presentation of an RCC has been reported in up to 25% of adult patients (4) but is less frequently reported in children. (9) Note that during the 2 years before discovery of the RCC, our patient's psychiatric and somatic symptoms were not controlled with antidepressant medications.

Asymptomatic patients with incidental discovery of a small cystic lesion can be observed. (1) For patients with progressive enlargement of their lesion, endocrinopathies, or visual disturbances, surgical intervention is warranted, with pathologic slides helping differentiate RCCs and ACPs. Most sellar/suprasellar tumors are approached via the

transsphenoidal route. The most common surgical strategy includes fenestration of the cyst, evacuation of cyst contents, and biopsy of the cyst wall. (1) Generally, there is minimal attempt to remove the cyst wall, and the sellar floor is left open to allow cyst drainage into the sphenoid sinus. This strategy relieves symptoms and has minimal associated pituitary dysfunction but has been associated with higher recurrence rates, approaching 30% in some series. (4) Complete resection is associated with lower recurrence rates, but there is a higher risk of pituitary dysfunction and cerebrospinal fluid leak. (1)

The patient was prescribed physiologic dosing of hydrocortisone (10 mg/m^2 per day) for secondary adrenal insufficiency, levothyroxine for central hypothyroidism, and desmopressin for central diabetes insipidus. Cyst removal was performed via the endoscopic endonasal transsphenoidal approach. On microscopic examination, intact fragments of cyst epithelium were composed of tall columnar cells with well-preserved apical cilia, a histologic finding consistent with RCC. (10) No foci of "wet keratin," stellate reticulum, or stratified squamous epithelium were present in the specimen, and, therefore, an ACP was much less likely. Repeated ophthalmologic testing with a Humphrey visual field study 3 months postoperatively reveals resolution of bitemporal superior quadrantanopsia. No residual cyst is detected on repeated MRI 5 and 18 months after neurosurgery (Fig, bottom row). Now nearly 13 years old and more than 18 months from the operative date, the patient has sustained resolution of headaches, improved energy and appetite, with normal mood and behavior off psychotropic medications. She requires ongoing replacement of hormones given central endocrinologic dysfunction and is maintained on hydrocortisone, levothyroxine, growth hormone, and desmopressin, with planned initiation of estradiol supplementation given inadequate pubertal growth secondary to hypogonadotropic hypogonadism.

Lessons for the Clinician

- Diligently following growth trajectory and Tanner staging for even subtle abnormalities may be critical in promptly diagnosing an underlying endocrinopathy, especially in the setting of unexplained electrolyte disturbance
- Only a minority of Rathke cleft cysts (RCCs) present in children; however, they are more likely to be symptomatic, in contrast to adults.
- The most common presenting symptoms of RCC include headache, visual disturbances, and endocrine dysfunction.
- Craniopharyngiomas manifest similarly to RCCs, and although each has characteristic radiologic findings, histopathologic analysis is needed to distinguish one from the other.
- Evacuation of cyst contents is the most common surgical approach, and cysts rarely recur. Complete cyst resection carries a higher risk of pituitary dysfunction and cerebrospinal fluid leak.

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