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Adolescent Anxiety or Polyendocrine Autoimmunity?

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The Centers for Disease Control and Prevention mental health 2005 to 2011 report identifies that 13% to 20% of US children experience a mental disorder each year with significant individual and public health, social, and economic consequences.[1] While attention deficit hyperactive disorder is the most common childhood neurobehavioral disorder (estimated prevalence 8.6%), childhood anxiety panic attack disorder (estimated prevalence 4.7%) commonly occurs or is misdiagnosed in presence of other medical conditions that include hyperthyroidism, hyperparathyroidism or abnormal serum calcium levels, pheochromocytoma, vestibular dysfunctions, seizure disorders, and cardiopulmonary conditions.[2-4]

Our teen female patient presented with panic attacks unresponsive to psychiatry consultation with short course of selective serotonin reuptake inhibitor therapy. Her family physician obtained basic metabolic blood tests and requested immediate attention of our medical center (University of Mississippi Medical Center [UMMC]) pediatric endocrine service to assess and correct her severe hypocalcemia.

This brief report calls attention to symptoms and associated medical conditions to consider early in differential diagnosis and management of adolescent behavior disorders. Our patient's clinical course is unusual in its presentation of panic attack symptoms with hypocalcemia, its rapid 6-month progression of multiple endocrinopathies, and transient hypercalcemia with onset of adrenal insufficiency. We summarize medical literature pertinent to our patient's rare polyendocrinopathy.

Methods

Our patient received appropriate medical care for her presenting symptoms, diagnoses, and treatment. Her medical chart was reviewed, and all of her health information was de-identified by her attending physicians prior to submission for publication.

Ethical Approval and Informed Consent

At each UMMC hospitals and clinics presentation, a caretaker signed with verbal patient assent or patient signed a UMMC routine Consent for Treatment, Authorization to Release Medical Information, and Assignment of Insurance Benefits for Hospitals and Physicians form. UMMC Human Research Office Self-Certification form was completed by authors asserting this is a single case report not meeting the 45 CFR 46.102(d) definition of human research and does not require institutional review board review. Preparation of this case report followed UMMC Human Research Office (Federal Wide Assurance No. 00003630) and Health Insurance Portability and Accountability Act.

Case Report

A 14-year-old female presented to her family physician complaining of recurrent panic attacks with poor school performance for about 8 weeks. Her attacks occurred mainly at school and lasted up to 30 minutes with dyspnea, intermittent eyes crossing, and stiffening of primarily her right arm. Her complete recovery took about 5 minutes. She also reported intermittent "bone aches" and bad headaches that were worse in the morning. The magnetic resonance imaging study of her head was normal. Her medical history was notable for poor tooth mineralization and recurrent candida vaginitis. Menarche occurred at 12 years of age with persistent irregular cycles. She reported no improvement in her panic attacks following 3 months psychiatry therapy that included 2-week trial of Paxil 10 mg tablet every

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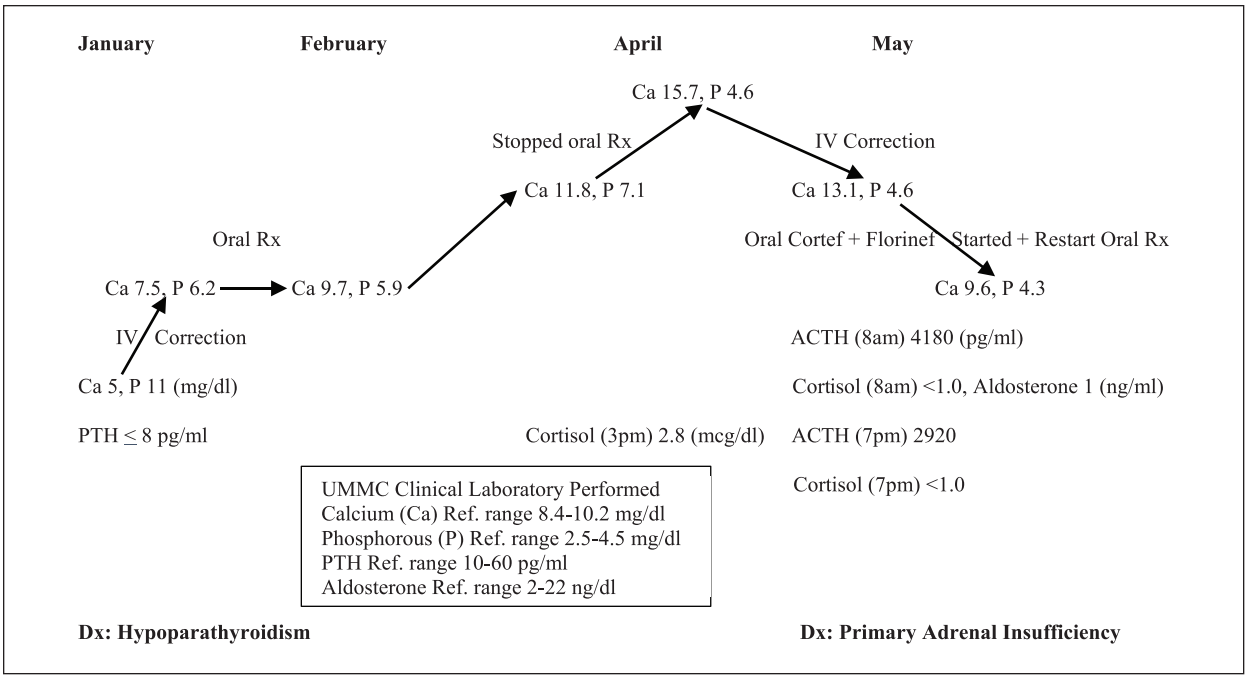

Figure 1. Evolution of adrenal insufficiency with hypoparathyroidism.

morning by mouth daily as prescribed by her family physician off-label at that time for pediatric use but supported by published clinical research on paroxetine (Paxil) treatment of anxiety disorder in 18-year-old and older adults.[5] Her physical examination was grossly normal (height 154 cm, weight 45 kg, body mass index 19 kg/m^2, blood pressure 109/52 mm Hg, pulse 100 beats per minute) except for eye twitching. As her family physician was about to adjust her Paxil at the recommended 2-week interval, her blood tests revealed severe hypocalcemia. Her family physician discontinued Paxil and requested direct admission to UMMC pediatric endocrine service for further management.

Her workup revealed low total calcium 5 mg/dL, high phosphorous 11 mg/dL, marginal low magnesium 1.2 mEq/L, and otherwise normal serum electrolytes with 25-hydroxy vitamin D 23 ng/mL (Reference [Ref] = 13-67 mg/dL; Figure 1). These results were consistent with primary hypoparathyroidism as her parathyroid hormone level returned less than 8 pg/mL. During her hospitalization, she responded to intravenous calcium without complications and was transitioned to oral calcium with 1,25-dihydroxyvitamin vitamin D analogue. Her outpatient child psychologist's records were not available, but our inpatient child psychology consult indicated that she was diagnosed with an anxiety disorder based on *Diagnostic and Statistical Manual of Mental Disorders* criteria prior to her hypoparathyroidism diagnosis. On discharge, her serum calcium 7.5 mg/dL and phosphorous 6.2 mg/dL were stable without reoccurrence of panic attacks, and she returned to her good school performance. Her parathyroid-directed antibodies returned consistent with autoimmune hypoparathyroidism. The family was informed of rare possibility for additional autoimmune endocrine and immune system dysfunction.

After 4 months of hypoparathyroidism therapy, she presented with vomiting and dehydration. Laboratory work showed hypercalcemia 11.8 mg/dL and hyperphosphatemia 7.1 mg/dL with stable electrolytes (Figure 1). Supplemental oral calcium was discontinued, but her calcium continued to rise to 15.7 mg/dL over the next 4 weeks. She was rehospitalized to monitor her medical compliance and recovery from hypercalcemia and dehydration with a 4 lb weight loss.

Her differential diagnoses for nausea and vomiting episodes included gastrointestinal (GI) inflammation and adrenal insufficiency (acute vs chronic).[6] Her Westergren sedimentation rates transiently rose to 47 mm/h (Ref = 5-19). Hepatic, antinuclear antibodies, and celiac disease panels returned negative. Her GI consultant–directed esophagogastroscopy returned nonspecific minor prepyloric erosions and edema without ulcerations or other GI pathology. One month prior to this admission, her late afternoon serum cortisol was 2.8 μg/dL. During this hospitalization, repeat cortisol levels were <1.0 μg/dL at 8 AM and 7 PM. These paired with adrenal corticotropic hormone levels of 4180 and 2920

Table 1. Autoimmune Polyglandular Syndrome Type 1 (APS-1) Frequency Major and Minor Clinical Features.[7].

Clinical Feature	Frequency (%)
Candidiasis	20-100
Hypoparathyroidism	65-95
Adrenal insufficiency	25-90
Intestinal complaints	8-75
Premature gonad failure	0-70
Autoimmune hepatitis	10-35
Pernicious anemia	0-32
Vitiligo	10-30
Malabsorption	8-28
Diabetes mellitus type 1	5-22
Hypothyroidism	0-20
Asplenia	0-15
Keratoconjunctivitis	0-10
Nail dystrophy	0-10

pg/mL, respectively, confirmed primary adrenal deficiency. Despite severe cortisol and mild aldosterone (1 ng/dL) deficiencies, her electrolytes and blood glucose levels remained within normal limits except for transient hypercalcemia (Figure 1). Her GI complaints and hypercalcemia resolved within a few days with intravenous hydration and start of daily oral hydrocortisone (Cortef) and aldosterone analogue (Florinef). Her oral calcium and vitamin D (Rocaltrol) medications were resumed (Figure 1).

The triad of hypoparathyroidism, adrenal insufficiency, and candidiasis were consistent with a genetic mutation subtype of autoimmune polyglandular syndrome (APS), likely type 1 (APS-1) or autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (Table 1). Blood sent for high-resolution genetic assessment returned homozygous for known APS-1 deletion of nucleotides 1094-1106 on chromosome 21 at 21q22.3.[7-9]

Pediatric endocrine service followed her until 18 years of age. During that time, her estradiol 4.3 ng/dL, luteinizing hormone 33.8 mIU/mL, and follicle-stimulating hormone 10.6 mIU/mL levels combined with her persistent irregular cycles were suggestive of emerging hypergonadotropic hypogonadism. Her pancreas- and thyroid-directed antibody panels remained negative without development of diabetes mellitus, thyroid dysfunction, or loss of visual acuity.

At 28 years of age, she presented with blurred vision and blind spots. Her visual acuity was 20/60 right eye and 20/50 left eye. Fundoscopy revealed presence of pigmented spicules and macular atrophy with attenuated retinal vessels consistent with pigmented paravenous chorioretinal atrophy. Optical coherence tomography and visual fields were normal. Antiretinal antibodies were positive, consistent with the autoimmune etiology of this disorder rarely associated with APS-1.[10] Over the next 2 years, her visual acuity decreased to 20/400 right eye and 20/80 left eye.

Discussion

Our teen female patient presented features consistent with panic attacks that reoccurred over several months during which she received psychiatry consultation without resolution. Her family physician obtained appropriate metabolic panel laboratory tests that revealed severe hypocalcemia requiring emergency inpatient care for uncomplicated recovery to normal serum calcium and diagnosis of hypoparathyroidism.

APS-1 is classically reported to present before 5 years of age with recurrent candidiasis preceding hypoparathyroidism and adrenal insufficiency usually prior to 15 years of age. The diagnosis of APS-1 is considered to be difficult at an early age when only one aspect of its associated polyendocrinopathy presents, and additional autoimmune conditions may take years to appear. Our patient's unusually rapid 6-month evolution from hypoparathyroidism with recurrent candidiasis to adrenal insufficiency and premature ovarian failure supports assessment and genetic confirmation for her APS-1 diagnosis. Her clinical course encourages early metabolic assessment when addressing adolescent behavior disorders and short-interval monitoring for APS.[7-15]

Our patient's lack of expressed hypoglycemia, electrolyte imbalance other than calcium and phosphorous, or aberrant skin pigmentation supported acute 1- to 2-month development of her adrenal insufficiency. Her hypercalcemia was unusual to associate with her onset of adrenal insufficiency and raised concern for medical compliance. However, her hypercalcemia likely reflected calcium intake for preexisting hypoparathyroidism with reduced glomerular filtration rate and hypovolemia due to GI complaints known to occur with adrenal insufficiency.[6,11]

APS-1 is rare with prevalence 1:90 000 to 1:200 000 but possibly 1:9000 or higher in some isolated groups or with a high degree of consanguinity not reflected in our patient's family pedigree. Polyglandular autoimmune syndromes tend to show a female predominance not seen with APS-1 as classically due to a homozygous (autosomal recessive) inactivating mutation in the autoimmune regulator gene, AIRE.[7-9,12-15]

APS is a set of rare genetic disorders historically evolving from Thomas Addison's 1849 description of unexplained deaths of patients with suprarenal (adrenal) disease and other features now recognized as autoimmune concerns: pernicious anemia and vitiligo.[16] Adrenal insufficiency, primary or secondary, tends to develop in an insidious manner if not first detected as an adrenal crisis

Table 2. Autoimmune Polyglandular Syndrome Type 1 (APS-1) Clinical Features and Associated Autoantibodies[7-11].

Clinical Feature	Associated Autoantibodies
Candidiasis	IL-22, IL-17F, myosin-9
Hypoparathyroidism	NACHT, NALPS, CaSR
Addison disease	CYPC17, CYP21, CYPSCC, CYP11A1
Autoimmune hepatitis	CYP-1A2, TPH, CYP-2A6, AADC
Diabetes mellitus	IA-2, GAD65, Anti-insulin, ICA512, ZNT8
Hypothyroidism	TPOAb, TGAb, TSHRAb
Hypergonadotropic hypogonadism	CYPC17, CYPSCC
Retinal degeneration	Antiretinal antibodies

(hypoglycemia, hyponatremia with hyperkalemia, cardiovascular collapse) precipitated by stress (eg, trauma, surgery, or serious infection). In the absence of an adrenal crisis, 50% of patients may have subtle signs and symptoms of Addison's disease for longer than 1 year prior to diagnosis: progressive weakness, lethargy, stomach complaints with nausea and vomiting, anemia, skin hyperpigmentation or vitiligo, and cardiovascular failure.[6,16]

APS-1 clinical diagnosis should include at least 2 of 3 primary features: candidiasis, hypoparathyroidism, and adrenal insufficiency (Tables 1 and 2). Since 1980, 2 major APS subtypes have been recognized to include Addison's disease with different genetic associations (APS-1 and APS-2) leading to current classification: APS-1 (diabetes mellitus type 1 occasional and late onset, thyroid disease unusual), APS-2a (with Addison's), and APS-2b (without Addison's). Immunogenetic studies associate human leukocyte antigen (HLA) class 2 genes with APS-2a and APS-2b. AIRE 21q22.3 gene mutations are associated with APS-1.[7-15]

Key Points

Anxiety disorders tend to develop in childhood about twice as often in females than males and may persist so that diagnosis of isolated anxiety disorder must reasonably exclude symptoms of substance abuse, patient's current medications, or another medical condition.[2-4] Endocrine and associated autoimmune conditions should be considered early when evaluating suspected adolescent behavior disorders. Clinicians should be mindful of potentially rapid multiple-organ autoimmune involvement to diagnosis an APS early and expedite successful management of anxiety and compliance with hormone replacement therapy as well as life-saving infection control.

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Author Contributions

WNS: Contributed to conception and design; contributed to analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
VVG: Contributed to conception; contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
TAM: Contributed to analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
GWM: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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