Spontaneous Adrenal Hemorrhage Associated with Transient Antiphospholipid Antibody in a Child

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Introduction

Acute adrenal crisis secondary to adrenal hemorrhage is well documented in the pediatric age group. It is most commonly seen in the newborn period secondary to prolonged labor and a traumatic delivery, usually of a large male infant.[1] It may occur also during an acute infection such as fulminating meningococcemia. There are reports[2-5] of adrenal hemorrhage occurring in patients with hemorrhagic diathesis (coagulopathies) and thromboembolic diathesis (antiphospholipid syndrome). However, adrenal hemorrhage has not been the sole presenting feature in the latter 2 situations. We describe an otherwise healthy 8-year-old female who presented with acute bilateral adrenal hemorrhage without any apparent reason and whose only demonstrable coagulation abnormality was the transient presence of antiphospholipid antibody and elevated activated partial thromboplastin time (aPTT).

Patient Report

An 8-year, 9-month-old girl presented with severe lethargy and unresponsiveness. She was in her usual state of good health 3 days before this episode. She had complained of nausea and abdominal pain for 2 days and had vomited 3 times the previous day. She had a low-grade fever and poor oral intake for 24 hours before admission. Her blood pressure was 110/62 mm Hg, her pulse was 150/min, and she was afebrile. Serum glucose concentration was 29 mg/dL (1.6 mmol/L). She had ketonuria. Other serum chemistries were sodium: 129 mEq/L (129 mmol/L), potassium: 5.1 mEq/L (5.1 mmol/L), chloride: 92 mEq/L (92 mmol/L), bicarbonate: 21 mEq/L (21 mmol/L), serum urea nitrogen: 17 mg/dL (6.1 mmol/L), creatinine: 0.6 mg/dL (53 mmol/L), and calcium: 10.2 mg/dL (2.6 mmol/L). Hemoglobin was 12.5 g/dL, hematocrit 43.8%, and white blood count was 12,500/mm^3. Urine toxicology screen was negative. She became responsive after receiving intravenous dextrose.

Her history was negative for hypoglycemia, lethargy, poor appetite, weight loss, salt craving, excessive tanning, nausea, and vomiting. There was no history of trauma. She was not taking any medications. The physical examination was unremarkable. Skin pigmentation was normal.

The hospital course was complicated by poor oral intake and continued vomiting. Hence she received continuous intravenous fluids. She continued to have

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mild fever and complained of mild periumbilical pain. She had orthostatic hypotension and a transient syncopal attack. Mild hyponatremia persisted [sodium: 132 mEq/L (132 mmol/L)]. Serum cortisol concentration at the time of hypoglycemia was 0.9 mcg/dL (24.8 nmol/L) [expected value during hypoglycemia >18 mcg/dL (496.6 nmol/L)] . Blood culture was negative. Radiographs of the abdomen and chest were negative for adrenal calcification, pulmonary infiltrates, or hilar lymphadenopathy or microcardia. The results of cosyntropin stimulation test are displayed in Table 1.

A Mantoux test and serum antiadrenal antibodies were negative. A peroxisomal panel was within normal limits. Bilateral adrenal hematomas were found on computed tomography (CT) (Figure 1). Glucocorticoid replacement therapy and fludrocortisone were started. She improved clinically, becoming more alert and responsive. Her oral intake improved, the abdominal pain resolved, and she did not have any further episodes of hypoglycemia or hypotension. Serum sodium also normalized [142 mEq/L (142 mmol/L)].

Baseline serum thyroxine concentration was 15.1 mcg/dL (194.3 nmol/L) (normal: 4–11 mcg/dL; 51.5–141.6 nmol/L), T_3 resin uptake 30.4% (normal 24–36%), and thyrotropin 1.7 uU/mL (normal 0.3–5 uU/mL). Following initiation of steroid replacement, the thyroxine concentration decreased to 13.7 mcg/dL (176.3 nmol/L), T_3 resin uptake was 27%, free T_4 1.46 ng/dL (18.8 pmol/L) (normal: 0.83–1.4 ng/dL; 10.7–18.0 pmol/L), and thyrotropin 0.5 uU/mL. At no time did she have any symptoms or signs of hyperthyroidism.

Table 1

RESULTS OF COSYNTROPIN STIMULATION TEST

Time [min]	0	60	Normals
Cortisol (mcg/dL)	1.2	1.0	>18 at 60 min
(pmol/L)	33.1	27.6	>496.8 at 60 min
Aldosterone (ng/dL)	<1.6	<1.6	
(pmol/L)	<44.4	<44.4	
Corticotropin (pg/mL)	459		0–46
(pmol/L)	101.1		0–10

Evaluation for coagulopathy revealed an elevated aPTT and elevated anticardiolipin antibodies (Table 2). Serum antinuclear antibody (ANA) and rapid plasma reagin (RPR)were negative. Antibody titers against *Borrelia burgdorferi* and HIV were negative. A repeat CT scan 2 months later revealed resolving bilateral adrenal hematomas (Figure 1). An abdominal ultrasound 6 months later revealed no calcifications or abnormalities in the suprarenal region. Serum corticotropin concentration at that time was 166 pg/mL (36.5 pmol/L) (normal: 7–28 pg/mL; 1.5–6.2 pmol/L) while was still receiving hydrocortisone and fludrocortisone, indicating persistent adrenal hypofunction. She has not subsequently developed any signs of other endocrinopathies or thromboembolic phenomenon. Twelve months later a repeat evaluation for anticardiolipin antibody was negative and the aPTT was normal.

Discussion

Primary acquired adrenal insufficiency (Addisons disease) results from destruction of the adrenal cortex. The etiology is either acute (due to adrenal hemorrhage) or chronic (autoimmune, tuberculosis, histoplasmosis, HIV). Currently autoimmune Addisons disease accounts for 85% of all cases of primary adrenal insufficiency.[6] Acute adrenal hemorrhage may occur with septicemia or after prolonged labor and a traumatic delivery, usually of a large male infant.[1]

According to Rao,[7] the adrenal glands are intrinsically vulnerable to hemorrhage because of several factors: extremely high rate of blood flow in the gland, a plethora of arteries supplying a gland drained by a single central vein, resistance to venous drainage in tributaries that have to pass between the longitudinal muscle bundles in the central vein, and a "vascular dam" caused by the relative paucity of venous

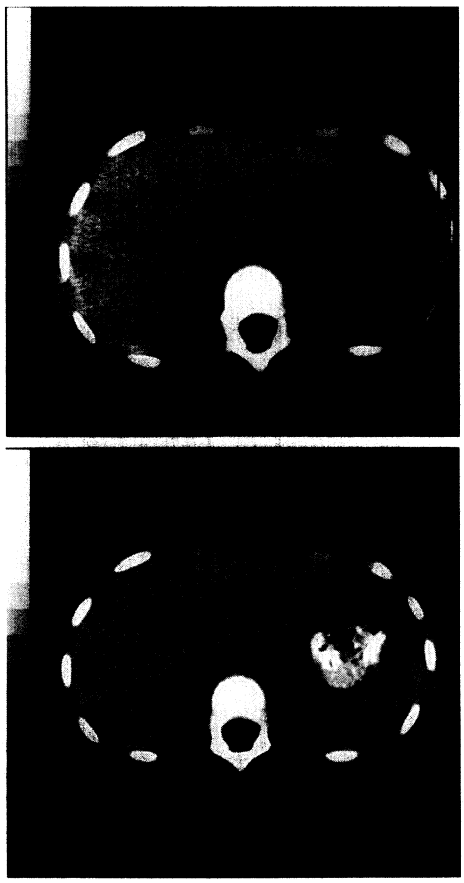

Figure 1. CT of adrenal glands. Top panel shows initial CT obtained several weeks after presentation. Adrenal glands are enlarged. Bottom panel shows repeat CT 2 months later showing resolution of the bilateral adrenal hemorrhages.

channels draining the highly vascular reticularis plexus at the corticomedullary junction.

As described by Rao,[7] the clinical features of adrenal hemorrhage are as follows: (1) Abdominal pain in about 67% of patients but with no distinctive character or location, abdominal signs like guarding, rigidity, and rebound present in only 15% of patients; (2) fever in 50% of patients but without a typical pattern; (3) neuropsychiatric manifestations like anorexia or fatigue in 12% of patients; (4) hypotension in 19% of patients.

Common laboratory features are hyponatremia, hyperkalemia, or azotemia (56% of patients) and a fall in hemoglobin concentration (>2 gm/dL) (51% of patients). Eosinophilia is not generally seen.

Our patient is unusual because she had massive bilateral adrenal hemorrhages in the absence of a preceding event such as sepsis, trauma, or disseminated intravascular coagulation. There have been case reports of adrenal hemorrhage in pediatric patients with antiphospholipid syndrome, but they also have had other features like venoocclusive phenomena or arterial thromboembolism.[2-4] Our patient had a slightly prolonged aPTT and mildly elevated anticardiolipin antibodies. She appeared to have had a transient coagulopathy secondary to antiphospholipid antibody. She did not fulfill the published criteria for the antiphospholipid antibody syndrome since she had no history of recurrent thromboembolic events and has not had any subsequent thromboembolic events for 18 months following the presenting event.[8]

The term *antiphospholipid antibody* includes both anticardiolipin antibodies and may also include antibodies to other phospholipids like phosphotidyl serine and phosphotidyl ethanolamine. The prevalence of anticardiolipin antibodies and lupus anticoagulant in pediatric systemic lupus erythematosus (SLE) is between 30% and 87%.[8] Our patient had no symptoms suggestive of SLE such as rash, photosensitivity, oral ulcers, arthritis, renal disorder, hematuria, hemolytic anemia, or seizure disorder, and antinuclear antibodies were negative. Therefore, she does not satisfy the criteria for SLE.

Drugs like chlorpromazine and infections like Lyme disease, syphilis, HIV, and adenovirus can induce anticardiolipin antibodies in children. These antibodies are usually produced in low titers and are transient.[8,9] We did not find serologic evidence of syphilis, Lyme disease, or HIV in our patient, and she did not have a history of recent drug exposure. We speculate that the transient antiphospholipid antibody present may have been secondary to a viral infection.

Our patient had transient elevations in total T_4 levels with normal

Table 2

EVALUATION FOR COAGULOPATHY

Test	Result			Normals
		6 mo. later	12 mo. later	
PT INR	1.0	1.0		1.0
aPTT [secs]	33.6			30.9
Repeat aPTT	30.2			29.8
	32.2			23–33
Anticardiolipin ab IgG [GPL]	17	8	12	0–14
Anticardiolipin ab IgM[MPL]	8	13	Negative	0–9
ANA	Negative			
Protein C antigen	97%			>70%
Protein C functional	107%			60–138
Protein S antigen	102%			>70%
Protein S functional	89%			>60%
Factor V Leiden mutation	Negative			Negative
Antithrombin III (mcg/dL)	29			19–30
Antithrombin functional	135%			80–120
Cysteine and homocysteine screen	Negative			Negative

PT=prothrombin time, INR=international normalized ratio, aPTT=activated partial thromboplastin time, ab=antibody, IgG=immunoglobulin G, ANA=antinuclear antibody.

thyrotropin. Hyperthyrotropinemia and hyperthyroxinemia may be seen in adrenal insufficiency. Our patient did not have any clinical evidence of thyroid disease, and her asymptomatic hyperthyroxinemia resolved on glucocorticoid therapy. The basis for abnormal results from thyroid tests in primary glucocorticoid deficiency is believed to be an elevation in thyrotropin secretion in primary adrenal insufficiency.[10,11]

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