Hypertrophic Obstructive Cardiomyopathy in an Infant With an Adrenocortical Tumor

abstract

Nonfamilial cardiomyopathies in childhood have been only sporadically ascribed to endocrine disorders. We report on a 4-month-old male infant presenting with Cushing’s syndrome associated with excessive body weight (8.9 kg; >97th percentile) and features of virilization (Tanner stage 2 for pubic hair development). Abdominal sonography showed a large adrenal tumor. Echocardiography revealed myocardial hypertrophy with severe subaortic obstruction. Blood tests showed excessive androgen and cortisol serum levels with absent circadian rhythm as well as suppressed corticotropin. Urine catecholamine levels were within the normal range. Tumor resection with general anesthesia was performed after preparation with antihypertensive and anticongestive drug therapy. Continuous intravenous hydrocortisone substitution was started intraoperatively and subsequently tapered and switched to oral administration after 12 days. A gradual reduction in glucocorticoid substitution and its discontinuation after a total duration of 9 months were well tolerated. Histopathologic workup revealed an adrenocortical tumor of intermediate dignity. Postoperative tumor staging excluded both residual primary tumor and metastases. Both a normalization of body weight and myocardial mass were observed. The present article is, to our knowledge, the first to describe severe hypertrophic obstructive cardiomyopathy caused by an adrenocortical tumor and provides novel detailed data on postoperative glucocorticoid management. Pediatrics 2013;132:e535–e539
Hypertrophic obstructive cardiomyopathy (HOCM) is a condition characterized by hypertrophy of the myocardium and consecutive obliteration of the left ventricular outflow tract (LVOT). It is most commonly ascribed to a number of genetic disorders, including sarcomeric mutations or storage diseases. The less common nonfamilial HOCM is an etiologically diverse entity and has been only sporadically ascribed to endocrine disorders.1

We report the case of a 4-month-old boy presenting with Cushing’s syndrome and severe HOCM due to an adrenocortical tumor (ACT).

**PATIENT PRESENTATION**

A white male was born to a 34-year-old primigravida in gestational week 38 + 6 by cesarean delivery due to premature rupture of the membranes; the pregnancy was unremarkable. Newborn physical assessment revealed an elevated birth weight of 4.4 kg (>97th percentile). Maternal history was negative for gestational diabetes but revealed breast cancer diagnosed at 27 years of age that had been successfully resected and subsequently treated with goserelin and tamoxifen. Echocardiography was performed postnatally and revealed a marginally increased septal wall thickness of 8 mm; however, abdominal sonography at that time was unremarkable. There was no family history of HOCM.

At 4 months of age the patient was referred for routine follow-up and sonography, which revealed a large mass in the right adrenal region. Echocardiography showed marked myocardial hypertrophy with a diastolic interventricular septal thickness of 18 mm, as well as systolic anterior movement of the anterior mitral leaflet and significant LVOT obstruction with a peak pressure gradient of 100 mm Hg at rest (Fig 1A). An electrocardiogram showed signs of left ventricular hypertrophy as well as monomorphic premature ventricular contractions. The boy had clinical signs of Cushing’s syndrome and virilization, including central obesity, buffalo hump, moon face, acne, hypertrichosis, and pubic hair (Tanner stage PH2). Cardiac auscultation revealed a systolic murmur over the left parasternal border. Body weight and length were 8.9 kg and 66 cm, respectively (both >97th percentile). Resting blood pressures averaged 110/65 mm Hg. N-terminal pro-brain-type natriuretic peptide was 31 437 ng/L. Endocrinologic workup revealed excess serum cortisol of 965 nmol/L without diurnal variation, suppressed corticotropin (<1.1 pmol/L), and elevated androgen levels (dehydroepiandrosterone-sulfate: 27 mmol/L; testosterone: 35 nmol/L; androstenedione: 401 nmol/L). Aldosterone levels were normal. Blood counts and routine blood chemistry were unremarkable. Urine catecholamines and neuron-specific enolase in the serum were normal, but urine C19-steroids and cortisol metabolites were markedly elevated. MRI of the abdomen revealed an inhomogenous tumor measuring $6 \times 5.9 \times 5.9$ cm, which was apparently confined to the right adrenal gland (Fig 2).

Antihypertensive and anticongestive treatment with furosemide (1 mg, 3 times daily) and atenolol (1 mg, twice daily) was immediately initiated. Tumor resection by right subcostal laparotomy was performed with general anesthesia after normalization of blood pressure. Hydrocortisone substitution was started intraoperatively at a dose of 60 mg/m² per day by continuous intravenous administration to prevent postoperative adrenal insufficiency.
myocardial thickness regressed to 6 mm, with the LVOT showing no signs of obstruction (Fig 1B). N-terminal pro-brain-type natriuretic peptide levels decreased to 148 ng/L. Dehydroepiandrosterone-sulfate levels are no longer measurable. Hydrocortisone substitution was gradually tapered over 9 months and discontinued when endogenous corticotropin secretion was reestablished, and normal function of the adrenal cortex was verified by low-dose corticotropin test (stimulated cortisol: 610 nmol/L). Features of Cushing’s syndrome are no longer evident, and the boy is showing adequate psychomotor development. The association of early-onset malignoma in the family prompted genetic analysis, which revealed germ-line mutation in exon 5 of the TP53 gene (c.395A>G, p.K132R).

DISCUSSION

ACTs are rare, occurring in only 0.3 per 1 million children and adolescents below the age of 15 years. In the majority of pediatric cases, despite the presence of clinical and/or histologic features of malignancy, the long-term prognosis is more favorable than in adults.2–4 Germ-line mutation of the TP53 gene, also referred to as Li-Fraumeni syndrome, is a well-known risk factor for the occurrence of ACT and is causal in 80% to 98% of cases.4–6 Clinical presentation of ACT typically results from the hormonal activity (excessive androgen and glucocorticoid release) of these tumors and includes features of virilization in 59% to 84% of cases, often combined with Cushing’s syndrome.2–5 Myocardial hypertrophy and especially HOCM as a clinically relevant organ manifestation of ACT seems to be an extremely rare phenomenon, and we failed to find any other reports previously describing this association.

Gessler et al7 reported a female patient diagnosed with Cushing’s syndrome due to adrenocortical nodular hyperplasia in her second week of life, showing echocardiographic evidence of concentric myocardial hypertrophy. After unilateral adrenalectomy, regression of body weight was observed within a few months. However, the authors provided no details on follow-up, in particular on the extent of myocardial hypertrophy before and after therapy. Notably, hydrocortisone substitution was quickly tapered and discontinued after only 2 weeks after surgery. Data from ventilated preterm infants treated with glucocorticoids for prevention of chronic lung disease suggest that myocardial hypertrophy may occur in up to 40% to 57% of cases within as little as 7 to 10 days, depending on the regimen administered and birth weight.8,9 Cases of HOCM are occasionally reported and indicate that resolution of myocardial hypertrophy can be expected within 3 to 6 weeks after discontinuation of steroid therapy.8–10 In our patient, normalization of pronounced cardiac hypertrophy took significantly longer, which could reflect a prolonged exposure to both androgens and glucocorticoids before surgery.

The mechanisms underlying glucocorticoid-induced myocardial hypertrophy are currently not completely understood.
Experimental trials in rats suggest a key role of the SGK1 gene in the morphologic changes induced by glucocorticoids in cardiomyocytes as well as an upregulation of the α-myosin heavy chain. The trophic effects of androgens on the myocardium are well known and frequently observed in athletes who use illicit anabolic steroids. Gender-specific variations in androgen profiles are responsible for differences in myocardial weight and repolarization time between males and females. Investigations in mammalian cardiomyocytes revealed that androgen receptors are already expressed in infant hearts, thus causing hypertrophy through both genomic and non-genomic mechanisms. It is likely that the combined effects of excess glucocorticoids and androgenic steroids led to the extreme myocardial hypertrophy observed in our patient.

The treatment of HOCM caused by autonomous cortisol release entails a number of clinical complications. Our patient presented with arterial hypertension and severe HOCM, which causes pressure overload of the left ventricle and, consequently, heart failure. Removal of the cortisol-releasing tumor, although curative in regard to the cardiomyopathy, may cause an adverse decrease in blood pressure and metabolic insufficiency through glucocorticoid withdrawal. Peripheral hypotension in HOCM is a formidable complication with a potentially fatal outcome due to compromised organ perfusion of the brain and myocardium. Therefore, during tumor surgery, hydrocortisone substitution was started by using a continuous intravenous stress dose regimen of 60 mg/m² per day, which was subsequently tapered to a maintenance dosage under serum cortisol surveillance (Fig 3). Although it has been suggested that cortisol levels during substitution are kept within the age-adjusted normal range, several authors have documented “relative adrenal insufficiency” in patients after prolonged hypercortisolemia. Accordingly, these individuals showed clinical signs of steroid withdrawal despite normal blood cortisol levels, which was attributed to cortisol resistance of the peripheral tissues. We therefore aimed to maintain serum cortisol within levels at or slightly above the upper physiologic range. No episodes of hypotension were observed, yet myocardial thickness showed regression within a few weeks after surgery. The data shown in Fig 3 are, to our knowledge, the first documentation of a dose-response relationship in an infant receiving intravenous hydrocortisone substitution.

Last, it is of particular interest that despite marked signs of Cushing’s syndrome, no alteration in longitudinal growth was noted in our patient. We suspect that the inhibition of longitudinal growth usually observed in hypercortisolemia was neutralized by the excessive production of androgenic hormones.

**CONCLUSIONS**

HOCM is a rare complication of hormone-releasing ACT. Although removal of the tumor is the causal therapy, glucocorticoid withdrawal is of particular concern due to potentially deleterious effects on hemodynamics. The present report suggests that close monitoring and hydrocortisone substitution to supranormal serum cortisol levels allows for rapid regression of myocardial hypertrophy without compromising myocardial perfusion and cardiac output.

**ACKNOWLEDGMENT**

We thank Alisa Alspach for revising the English text.

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Pediatrics 2013;132;e535; originally published online July 8, 2013;
DOI: 10.1542/peds.2012-2692
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