Transient hypertrophic cardiomyopathy and hypertension associated with hydrocortisone in preterm infant
A case report
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Abstract
Rationale: Hypertrophic cardiomyopathy (HCM) is a heterogeneous, usually familial disorder of heart muscle. The hypertrophic form of cardiomyopathy is frequently genetic, or as part of several neuromuscular disorders. In neonates, especially prematurity, HCM could also be secondary to corticosteroid treatment.

Patient concerns: We reported here a 34 weeks gestational age preterm infant presented with profound cardiomegaly after multiple doses of hydrocortisone used to treat blood pressure instability associated with septic shock and persistent pulmonary hypertension (PPHN).

Diagnosis: Patient presented auscultation of a grade III/IV harsh systolic ejection murmur from day 14, which was absent before. Profound cardiomegaly was indicated at chest film at day 30. Echocardiography showed severe thickening of the IVS (13.8 mm, z score=8.29) and mild thickening of the posterior left ventricular wall (LVPW, 6 mm).

Interventions: Propranolol and captopril were started along with supportive care. The patient was also admitted to NICU for further treatment with 24-hour Holter electrocardiographic monitoring.

Outcomes: A reversible course was observed without left ventricular outflow tract obstruction nor arrhythmias within 4 weeks.

Lessons: The risk/benefit ratio must be carefully considered when corticosteroids are used in prematurity. Monitors such as echocardiography and electrocardiograph should be conducted in order to guide cardiovascular management. Systematic surveys of the incidence of cardiac complications in a larger population of preterm infant treated with corticosteroid are needed in the future.

Abbreviations: AO = aorta, COA = aortic coarctation, HbA1c = glycated hemoglobin, HCM = hypertrophic cardiomyopathy, HFOV = high-frequency oscillatory ventilation, HC = hydrocortisone, IVS = interventricular septum, LA = left atrium, LVOT = left ventricular outflow tract, LVPW = posterior left ventricular wall, MAP = mean arterial pressure, PAP = pulmonary artery pressure, PDA = patent ductal arteriosus, PPHN = persistent pulmonary hypertension, PW = posterior wall, TTE = transthoracic echocardiogram, UAC = umbilical artery catheter, UVC = umbilical venous catheter.

Keywords: hydrocortisone, hypertrophic cardiomyopathy, neonatal intensive care, septic shock

1. Introduction
Hydrocortisone (HC) is widely used in infants with increased inotropic support in septic shock and severe pulmonary disease.[1] The most recent Surviving Sepsis Guidelines use the term “catecholamine resistant shock” and recommend consideration of corticosteroids at this point.[2] However, question still needs to be resolved regarding the appropriate target population. In certain subgroups, increased risks of mortality, suppression of adaptive immunity, and secondary infections from corticosteroid administration have been suggested in several retrospective controlled trials (RCTs) in pediatric critical care.[3,4] Herein, we present a preterm infant with transient myocardial hypertrophy after multiple dose of hydrocortisone used to treat septic shock.

2. Case report
A 2260-g male infant was born at 34 weeks of gestation via caesarean section due to central placenta previa with hemorrhage to a 36-year-old multipara whose pregnancy was complicated with hyperthyroidism. Full dose of dexamethasone was given to the mother prior to delivery. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. The patient was admitted to the...
neonatal intensive care unit and intubated because of respiratory distress within the first 30 minutes of life. Pulmonary hemorrhage presented shortly after high-frequency oscillatory ventilation (HFOV). Inhalational nitric oxide was applied because of PPHN from day 3 to day 7. He received 2 doses of surfactant, umbilical venous catheter (UVC), and umbilical artery catheter (UAC) were conducted thereafter to monitor central artery pressure.

During the first 3 days, HC 2mg/kg q8h was given intravenously because of circulatory failure indicated by hypotension responsive to substantial fluid administration and intensive inotropic support. When the epinephrine and dopamine requirement were reduced, HC was weaned gradually over a period of 5 days. The mean arterial pressure (MAP) raised up to 92mmHg from day 7 and remained at 85 ± 7.4mmHg until discharge. The patient also accepted blood exchange and albumin (2g as a total dose) because of hyperbilirubinemia (greatest indirect bilirubin 434μmol/L).

Acute hypokalemia arised on day 14, serum potassium decreased to as low as 2.1mmol/L. Potassium replacement was given as 0.3 mmol/kg/h intravenously, as well as oral repletion 4 mmol/kg/d in divided doses. Serum potassium was between 2.8 and 3.3mmol/L in the following 2 weeks and remain normal thereafter.

Fetal echocardiography had been performed at 24 weeks of gestation, which showed a structurally normal heart without ventricular hypertrophy. The first pediatric cardiology consultation was requested at day 1. Transthoracic echocardiogram (TTE) revealed 3mm right-to-left shunting of blood across the foramen ovale and a large patent ductal arterious (PDA) with bidirectional shunting. The second TTE, performed at day 3, indicated mean pulmonary artery pressure (PAP) 35mmHg, LVEF 67% and similar atrial left-right shunt and patent ductal shunt when PPHN was persistent. At day 11, PPHN was ameliorated clinically, and the mean PAP had decreased to 23 mmHg suggested by 3rd TTE. The thickness of the interventricular septum (IVS) was normal at all these abovementioned TTE.

Echocardiography was repeated at day 30 because of profound cardiomegaly indicated at chest film and auscultation of a grade III/IV harsh systolic ejection murmur. This TTE showed severe thickening of the IVS (13.8mm, z score = 8.29) and mild thickening of the posterior left ventricular wall (LVPW, 6mm). Thicken of the ventricle affect the septum more than the ventricular free wall (IVS/LVPW 2.3, Fig. 1A and B). For children, IVS z-score of ≥2 related to body surface area is compatible with the diagnosis of hypertrophic cardiomyopathy. Outflow tract obstruction was not observed, with a peak velocity of 0.85 m per second. Aortic coarctation (COA) was ruled out. Prenatal history was negative for maternal risk factors as well as the familial history regarding genetic and metabolic diseases, sudden death, or syncope history. Maternal oral glucose tolerance test and glycated hemoglobin (HbA1c) were normal (Fig. 2).

Propranolol (0.2mg q8h) and captopril (0.02mg q8h) were administrated. 24-hour Holter electrocardiographic monitoring

Figure 1. Cardiomyopathy and hypertension track against the steroid dose. Hydrocortisone (2 mg/kg) was administrated in the first 5 days, duration shown as blue shadow in the chart.
demonstrated no arrhythmia. Serial transesophageal echocardiograms were performed the next few weeks. Thickness of the IVS decreased to 3mm progressively on day 60 (Fig. 1C and D). Except increased MAP, the baby remained completely asymptomatic. Supplemental oxygen was discontinued on the 30th day. Tandem mass spectroscopy analysis was normal. Exome sequencing targeting over 4000 genes was negative. The patient was discharged from hospital at 45th of life. At post-discharge follow-up, MAP was 65mmHg 60th postnatal day, cardiologic evaluation was normal.

3. Discussion

This report provides evidence that HC treatment is associated with hypertrophic cardiomyopathy (HCM) in prematurity. It is a well-established notion that HCM is the most common of the genetic cardiovascular diseases, caused by a multitude of mutations in gene encoding proteins of the cardiac sarcomere. Eleven mutated genes, most commonly encoding beta-myosin heavy chain, are presently associated with HCM, accounting for about 50% patients. Other causes may include non-sarcomeric protein mutations cause storage diseases that are phenocopies of sarcomeric HCM and require molecule diagnosis, namely, Fabry disease, Pompe disease, Friedreich ataxia, mitochondrial disorders, and medications such as tacrolimus. Several epidemiologic studies have reported a prevalence of the HCM phenotype as 2%, however, it is notable that most affected individuals remain asymptomatic and unidentified. Notably this condition is No. 1 cause of sudden death in the young, including competitive athletes. On the other hand, myocardium of prematurity is susceptible. In this population, dietary de...

Figure 2. Postnatal TTE at 30 days (A, B) and 60 days (C, D) of life. A, Parasternal long-axis view showing the severely narrowed left ventricular cavity as well as the hypertrophic interventricular septum. IVS/LVPW: 2.3; B, Parasternal 4 chamber view with color-flow Doppler showing no restriction of flow through the left ventricular outflow tract. EF 51%; C, Significant remission of left ventricular hypertrophy. D, Improvement of septal configuration. AO=aorta; IVS=interventricular septum; LA=left atrium; LVID=left ventricular outflow tract; PW=posterior wall.
HCM. The goal of hypertrophic cardiomyopathy treatment is to relieve symptoms and prevent sudden cardiac death in people at high risk. Medications such as beta blockers and calcium channel blockers are used to reduce myocardial oxygen demand and to slow the heart rate, therefore improve the compliance. Other treatments include septal myectomy or ablation, and implantable cardioverter-defibrillator. HC-induced HCM is usually a benign condition and was resolved a few weeks after discontinuation, furthermore, none of case in the literature present hypertension related to HCM. The precise incidence is lacking, however, the frequency and severity of myocardial hypertrophy may increase with dose and duration of HC treatment, infants receiving insulin in addition to HC may present in greater level of hypertrophy.

In conclusion, we strongly recommend that the risk/benefit ratio must be carefully considered when corticosteroids are used in neonatal septic shock, especially in prematurity. Since HCM is associated with lethal arrhythmias in some cases, adequate monitor such as echocardiography and electrocardiograph should be conducted in order to guide cardiovascular management. Novel therapeutic approaches to be applied in controlling its harmful consequences are suggested.

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