

Prenatal Exposure to Methyldopa Leading to Hypertensive Crisis and Cardiac Failure in a Neonate

abstract

A 2-week-old infant with normal intracardiac anatomy presented to the emergency department in a hypertensive crisis with acute cardiac failure. Despite extensive evaluation, no underlying disease was found. The patient's hypertension and cardiac dysfunction resolved after 1 week of supportive care in the PICU, and she was discharged within 2 weeks of presentation. The patient's history revealed transplacental exposure to the α -adrenergic agonist methyldopa for 10 weeks before delivery. Her age at presentation and the self-limited nature of cardiac sequelae with complete resolution of cardiac dysfunction suggest withdrawal effects from this exposure. Whereas the rebound hypertensive effects of α -adrenergic agonists are well established in the adult population, this report shows an unusual adverse outcome of in utero exposure to methyldopa. *Pediatrics* 2014;133:e1392–e1395

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KEY WORDS

hypertension, methyldopa, withdrawal, heart failure, newborn

ABBREVIATION

PIH—pregnancy-induced hypertension

Dr Su is the pediatric cardiology fellow who was involved in the reported patient's medical management and she drafted the initial manuscript; Dr Tang is the clinical pharmacist who was involved in the reported patient's medical management and he contributed his expertise in pharmacodynamics in the discussion portion of the manuscript; Dr Rivero is the pediatric intensivist who was involved in the reported patient's medical management and she critically reviewed the manuscript; Dr Bar-Cohen is the pediatric cardiology attending who was involved in the reported patient's medical management and he was the primary editor of the initial manuscript and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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Neonatal hypertension is exceedingly rare and is estimated at 0.2% of otherwise healthy newborns in the United States.¹ Because of its low incidence, the American Academy of Pediatrics does not recommend routine blood pressure monitoring in children until 3 years of age, unless preidentified risks are present. Such risk factors include known congenital heart disease, renal disease or family history of renal disease, and other systemic illnesses associated with hypertension.² Additionally, iatrogenic factors, such as medications, may occasionally cause hypertension in young children. We present a unique case of severe hypertension in an otherwise healthy full-term infant due to withdrawal effects of prenatal exposure to methyldopa.

PATIENT PRESENTATION

The patient is a female infant born at 37 weeks' gestation to a 21-year-old gravida 1, para 0 woman via cesarean delivery for pregnancy-induced hypertension (PIH) and a nonreassuring fetal heart rate pattern. The mother received prenatal care throughout her pregnancy, which was complicated only by the PIH, and was started on 500 mg of methyldopa twice daily at 27 weeks' gestation. Due to persistent hypertension, the dosage was increased to 500 mg 3 times per day at 30 weeks' gestation, which adequately controlled PIH for the remainder of the pregnancy. There was no other history of maternal illness or exposures (including no antenatal steroid use). Serial prenatal ultrasound images were normal, including no abnormalities of the kidneys as well as normal fetal cardiac anatomy and function. Upon delivery, the patient was small for gestational age (birth weight of 2045 g; fifth percentile) and was admitted to the NICU for respiratory distress, hyperbilirubinemia, and hypoglycemia. A septic workup was performed with

initiation of ampicillin and gentamicin, and the antibiotics were continued for 48 hours with close monitoring. An echocardiogram was performed during her hospitalization, which revealed a small patent ductus arteriosus and a patent foramen ovale but otherwise normal cardiac anatomy and function. Blood pressures and cardiac function appeared normal throughout this initial NICU course, and renal function was assessed as normal with an appropriate creatinine level of 0.5 mg/dL and normal electrolytes upon discharge, with no urine output abnormalities reported. Cultures from her septic workup were negative, and she was discharged from the NICU at 1 week of age.

At 2 weeks of age, the patient presented acutely to the emergency department with difficulty feeding, dyspnea, and hypoxia with an oxygen saturation of 70% on room air. She was afebrile but was found to be hypertensive with a blood pressure by cuff of 133/103 mm Hg and was tachycardic with a heart rate of 182 beats per minute. A chest radiograph was performed, which revealed cardiomegaly (Fig 1). An echocardiogram was obtained, which showed severely depressed biventricular function (fractional shortening

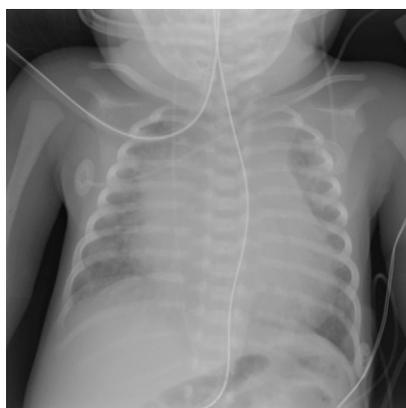


FIGURE 1

Chest radiograph at the time of initial presentation to the emergency department revealed cardiomegaly and diffuse pulmonary edema consistent with cardiac failure.

of 9% with an ejection fraction of 21%) without significant ventricular dilation. Pulmonary hypertension was also suggested by interventricular septal flattening and moderate tricuspid valve regurgitation with a peak gradient of 70 mm Hg. A patent foramen ovale was noted, but there were no additional anatomic defects. Her B-type natriuretic peptide was >5000 pg/mL (normal: <100 pg/mL), creatinine kinase was 569 U/L (normal: <230 U/L), and troponin-I was 0.17 ng/mL (normal: <0.05 ng/mL). She also had transaminitis with an aspartate aminotransferase of 1027 U/L (normal: 9–80 U/L) and an alanine aminotransferase of 376 U/L (normal: 3–45 U/L). Her electrolyte panel, including serum urea nitrogen of 20 mg/dL and creatinine of 0.38 mg/dL, was within the normal range. Given the patient's tenuous hemodynamic status with evidence of end-organ involvement, she was intubated, sedated, and admitted to the PICU for further evaluation and management.

In the PICU, an arterial line was placed for monitoring, which confirmed severe hypertension. She was started on nitroprusside and milrinone continuous infusions, which effectively controlled her hypertension. An extensive evaluation was performed to elucidate the cause of her acute hypertensive crisis. Results of her newborn screen were normal. A metabolic workup, including urine organic acids, plasma amino acids, free and total carnitine levels, and quantitative acylcarnitine profile, was normal. A head ultrasound was obtained, which showed no evidence of intracranial hemorrhage or other abnormality. Endocrine studies including thyroid function tests, cortisol, and lipid panel were unremarkable. Extensive renal studies were performed, and urine catecholamines, serum urea nitrogen, and blood and urine creatinine levels were found to be

normal. Urinalysis with microscopy initially revealed a moderate amount of occult blood in the urine, which quickly cleared as the patient's hypertension was controlled. The patient's urine output remained normal throughout the hospitalization. A renal ultrasound showed normal size and appearance of both kidneys with no evidence of renal artery stenosis. A rheumatologic evaluation ruled out systemic vasculitis and autoimmune disease. Furthermore, there was no family history of cardiac disease, autoimmune disorders, or early deaths. There were no reports of sick contacts, and the patient did not display any symptoms of infectious illness around the time of presentation. Despite a low suspicion for infection, a thorough infectious workup was performed including complete blood count with manual differential, blood and urine cultures, respiratory viral panel, erythrocyte sedimentation rate, and C-reactive protein. There was no evidence of inflammation or infectious involvement.

With supportive care of nitroprusside and milrinone infusions over the next several days, the patient's hypertension resolved and serial echocardiograms showed improvement followed by complete normalization of heart function (with a fractional shortening of 38.2% by 3 weeks of age). Her B-type natriuretic peptide, cardiac enzymes, and liver enzymes also normalized over the course of her hospitalization. She was discharged from the hospital at 4 weeks of age and has been followed closely by her pediatrician with no known recurrence of hypertension. An echocardiogram repeated 2 months after discharge again showed normal function.

DISCUSSION

In light of the acute presentation and self-limited nature of our patient's hypertension and cardiac dysfunction

with no evidence for other underlying disease upon extensive workup, we concluded that her acute hypertensive crisis and subsequent heart failure were due to withdrawal symptoms from maternal methyl dopa. The mother was on a relatively high dose of methyl dopa at 500 mg 3 times per day (the usual starting dose is 250 mg 2–3 times per day), and the patient was exposed to this medication in utero during the last 10 weeks of gestation. Rebound hypertension due to the withdrawal effects of α -agonists, including methyl dopa, has been well-documented as early as the 1970s. This report, however, is the first apparent documentation of this rebound phenomenon to occur from transplacental exposure to methyl dopa.

Methyl dopa has been assigned as a category B drug by the US Food and Drug Administration and is frequently used for the treatment of PIH. The drug crosses the placenta and has been found to cause mild hypotension in neonates with prenatal exposure. The mechanism of action of methyl dopa depends on its metabolism in the liver and intestines to α -methyl norepinephrine, which acts as a "false neurotransmitter." By competitively inhibiting the sympathetic effects of norepinephrine, it decreases systemic arterial pressures and also decreases plasma renin activity.³ Both methyl dopa and α -methyl norepinephrine are renally excreted.⁴ In adults with normal renal function (glomerular filtration rate: 90–120 mL/min), elimination is completed in 24 to 48 hours and rebound effects from chronic therapy have been reported within 48 hours, most prominently manifested by tachycardia and hypertension.⁴ The average glomerular filtration rate of a neonate is much lower, and although it rapidly rises during the first several weeks of life, it does not reach normal adult levels until several months of age.⁵ Furthermore, neonates often show immature liver function, which

was manifested by symptoms of hyperbilirubinemia and hypoglycemia in our patient. The relative impairment of both metabolism and clearance of methyl dopa likely led to accumulation of the drug and its active metabolite at high levels for a prolonged period (possibly >1 week postnatally). As the methyl dopa gradually cleared, our patient likely developed symptoms of methyl dopa withdrawal, manifested by tachycardia and a hypertensive crisis ultimately leading to acute heart failure.

Although it is difficult to prove definitively that the patient's hypertensive crisis and hence heart failure were caused by methyl dopa withdrawal, her extensive inpatient evaluation excluded a host of other potential causes of hypertension (including other neurologic, cardiac, renal, endocrine, rheumatologic, and infectious abnormalities).⁶ Additionally, the self-limited nature and complete resolution of the patient's symptoms without treatment of other underlying pathology support the likelihood that the patient's hypertension and subsequent cardiac dysfunction were caused by a transient and likely extrinsic source. Altogether, the patient's prenatal history of methyl dopa exposure, the normal neonatal physiology of depressed liver and renal function, and subsequent self-limited acute hypertensive crisis all fit within the pharmacokinetics of methyl dopa and strongly support our theory of α -adrenergic withdrawal.

This report shows potentially dangerous sequelae of methyl dopa exposure in the perinatal period. Current American Academy of Pediatrics recommendations for healthy newborns include an initial well-child visit at 2 weeks of age. Routine blood pressure measurements, however, are not obtained until the 3-year visit unless preidentified risks suggest a need for earlier blood pressure measurements.² As a result,

milder degrees of hypertension, including rebound effects from prenatal methyldopa exposure, may currently be under-recognized in the infant population. On the basis of this report, we would advocate for early blood pressure screening

(including at the 2-week well-child visit) when there is a prenatal history of methyldopa exposure. When these blood pressure measurements are outside of normative blood pressure values for age,⁶ we would advocate for closer monitoring

and possibly treatment. This more aggressive surveillance may improve early recognition of symptoms from methyldopa withdrawal and may allow for timely therapy and prevention of potential cardiac failure.

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