3 Respiratory Distress and Tachycardia in a Preterm Neonate

Andrew W. McCrary, MD,* Laura C. Page, MD,† Gregory H. Tatum, MD,* Rachel G. Greenberg, MD, MHS,‡ Stephanie Burns Wechsler, MD,*§ Pinar Gumus Balikcioglu, MD†

*Divisions of *Pediatric Cardiology, †Pediatric Endocrinology, ‡Neonatal-Perinatal Medicine, and §Medical Genetics, Department of Pediatrics, Duke University Medical Center, Durham, NC*

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PRESENTATION

A 31-week-gestation male infant is delivered vaginally in the setting of preterm labor and chorioamnionitis. The pregnancy was remarkable for late prenatal care, but no other complications. Maternal antenatal testing results were normal and the mother denied any significant medical history. The infant is initially stunned, but quickly recovers, with Apgar scores of 1 and 7 at 1 and 5 minutes, respectively. His size is appropriate for gestational age and his vital signs in the intensive care nursery include a temperature of 98.8°F (36.5°C), pulse of 172 beats/min, right lower extremity blood pressure of 76/34 mm Hg, respiratory rate of 62 breaths/min, and oxygen saturation of 98% on nasal continuous positive airway pressure support at 5 cm H_2O and 21% fraction of inspired oxygen. On examination, the infant's anterior fontanelle is soft, flat, and approximately 1 fingertip in size. His lungs are clear despite a mildly increased respiratory effort, including grunting and subcostal retractions. He has normal first and second heart sounds, a gallop rhythm, and no murmurs, and his liver is palpable 4 cm below the right costal margin.

On investigation, chest radiography demonstrates an enlarged cardiac silhouette (Fig 1), and echocardiography shows findings consistent with restrictive cardiomyopathy, normal systolic function, but impaired diastolic function (Fig 2). Given this rare finding, pediatric cardiology is consulted, which recommends conducting a comprehensive cardiomyopathy genetic testing panel. During his first week after delivery, the infant develops frequent ventricular ectopic beats and mild hypotension, necessitating volume resuscitation. His baseline heart rate shows a higher trend, toward a mean of 200 beats/min, and his tachycardia fails to respond to multiple fluid boluses. The team is also unable to wean him off the respiratory support. A milrinone infusion is started to relax the myocardium and augment cardiac output.

DISCUSSION

Given the infant's persistent tachycardia, thyroid disease is considered and evaluated. The thyrotropin level is decreased at 0.01 μIU/mL (normal, 0.34–5.66 μIU/mL) and the levels of total triidothyronine (total T_3) and free thyroxine (fT_4) are markedly elevated (280 ng/dL [4.3 nmol/L; normal, 80–178 ng/dL,

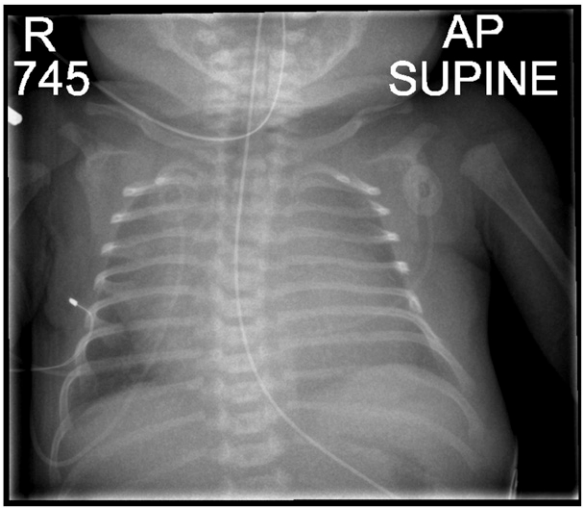

Figure 1. Chest radiograph demonstrating enlarged cardiac silhouette obscuring lung fields.

1.2–2.7 nmol/L] and 5.83 ng/dL [75 pmol/L; normal 0.52–1.21 ng/dL, 6.7–15.5 pmol/L], respectively). Although his mother again denies medical problems, the team suspects neonatal Graves disease and starts methimazole and propranolol.

The infant's heart rate normalizes on treatment for hyperthyroidism and he quickly weans off respiratory support and milrinone (Fig 3). Repeat echocardiography demonstrates improving diastolic function. Interestingly, the comprehensive cardiomyopathy panel returns with a mutation in the *RYR2* gene. Mutations in the *RYR2* gene have been associated with increased risk of developing catecholaminergic polymorphic ventricular tachycardia as well as arrhythmogenic right ventricular cardiomyopathy. However, the results of a functional analysis show that this infant's mutation is unlikely to have clinical significance.

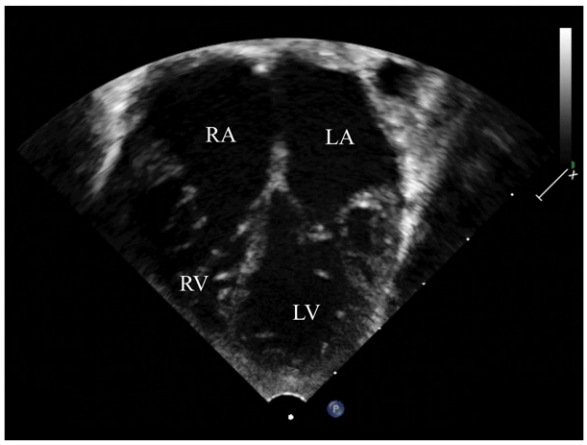

Figure 2. Apical 4-chamber echocardiogram demonstrating enlarged right and left atria bilaterally.

Before discharge, propranolol is discontinued and the infant's diastolic function and chamber sizes completely normalize. His mother is found to have active Graves disease and a goiter that has been covered by scarves and clothing with high necklines. The infant's methimazole is discontinued at 5 months of age and he has not had any further thyroid dysfunction.

The Condition

Neonatal Graves disease is a rare disorder that occurs when maternal thyrotropin receptor antibody (TRAb) crosses the placenta to reach the fetus. The estimated incidence of neonatal Graves disease is 1 in 25,000 to 50,000; only 0.2% of pregnant women have Graves disease and only 1% to 5% of their infants develop neonatal hyperthyroidism. (1)(2) Clinical manifestations of neonatal Graves disease include irritability, hyperactivity, flushing, poor weight gain, tachycardia, hyperthermia, diarrhea, frontal bossing, triangular facies, small anterior fontanelle and less commonly, heart failure, exophthalmos, cholestasis, thrombocytopenia, and hyperammonemia. (1)(2)(3)(4) A goiter is another sign of neonatal Graves disease, but can be difficult to detect in neonates. Therefore, thyroid ultrasonography should be used in suspected cases. (5) While reversible dilated cardiomyopathy can be seen in thyrotoxicosis, restrictive cardiac physiology, as was seen in this case, has not been described previously. (6)

Diagnosis

The timing of neonatal symptom development depends on the mother's use of an antithyroid medication such as methimazole. In the case of untreated mothers, including those who have had thyroidectomies or radioactive iodine ablation, the neonate may be symptomatic at birth and have abnormal thyroid function tests within the first week after delivery. (5) Conversely, infants born to mothers taking antithyroid medications may not manifest symptoms until 1 to 3 weeks after birth because of the drug's ability to cross the placenta. Importantly, infants with neonatal Graves disease may be euthyroid on the state newborn screen.

Laboratory evaluation can assist in the diagnosis and help predict the clinical course. Thyroid stimulating index assays specifically detect the presence of stimulating antibodies by measuring cyclic adenosine monophosphate production. (7) TRAb assays are competition-based, meaning they detect the presence of TRAb but cannot distinguish between stimulating, blocking, and neutral antibodies. (7) A negative TRAb finding in an infant is reassuring against future

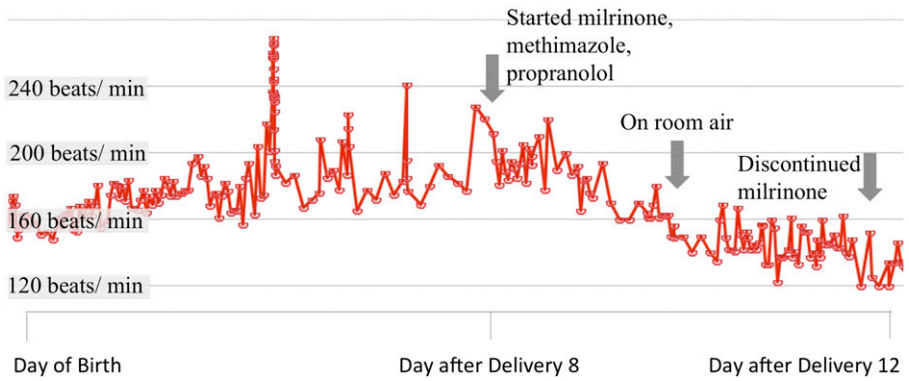

Figure 3. Heart rate trend from birth to 12 days after delivery.

development of neonatal Graves disease, and these infants can have standard pediatric care without additional thyroid monitoring. (5) Not surprisingly, high maternal serum TRAb levels late in pregnancy increase the likelihood that an infant will develop neonatal Graves disease. (5)

Management

Infants with neonatal Graves disease are commonly treated with a β-blocker and an antithyroid medication. (3) Methimazole is the preferred pediatric antithyroid agent because propylthiouracil carries a black box warning for hepatotoxicity. (8) More severe cases of neonatal Graves disease may require iodine (Lugol solution) to inhibit thyroid hormone release and/or glucocorticoids to reduce the conversion of fT_4 to the more active T_3. (9)(10)

Infants with neonatal Graves disease should be closely followed by a pediatrician and pediatric endocrinologist to monitor weight gain and thyroid function tests. Maternal TRAb levels in the infant typically wane between 3 and 12 weeks, and in most infants, the disease resolves spontaneously during this period, allowing methimazole to be discontinued. (1) The transient nature of neonatal Graves disease should be emphasized to parents because frequent laboratory evaluations are necessary to ensure that the infants do not become hypothyroid with methimazole treatment.

Lessons for the Clinician

- Vital sign abnormalities may be the first indicator of underlying thyroid disease.
- Neonatal Graves disease can present various phenotypes. Cardiac manifestations may be tachycardia alone, but evidence of cardiomyopathy (dilated or restrictive) is possible.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the anatomy and pathophysiology (including genetics) of an infant with a condition affecting myocardial performance.
- Identify the etiology, clinical manifestations, laboratory features, and management of neonatal thyrotoxicosis.

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Case 3: Respiratory Distress and Tachycardia in a Preterm Neonate

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