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Letter to the Editor
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Concurrence of Persistent Pulmonary Hypertension of the Newborn, Myocardial Ischemia, Supraventricular Tachycardia, and Congestive Heart Failure as a Harbinger of Neonatal Graves' Disease

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INTRODUCTION

Neonatal Graves' disease (NGD) is a rare disease affecting approximately 1 of 50,000 neonates, and most commonly caused by transplacental passage of thyroid stimulating immunoglobulin (TSI) from the mother to the fetus.[1] A diagnosis of Graves' disease (GD) can usually be made by characteristic clinical manifestations of hyperthyroidism.[1] However, a constellation of persistent pulmonary hypertension of the newborn (PPHN), myocardial ischemia (MI) without coronary artery disease, supraventricular tachycardia (SVT), and congestive heart failure (CHF) has never been reported simultaneously in NGD in the English literature.[2-5] We reported here a 12-day-old baby boy, born of a 34-year-old mother with unquenched or refractory hyperthyroidism incriminating GD, presenting postnatally with tachycardia, tachypnea, and systemic hypertension due to a flagrant constellation of PPHN, MI, SVT, and CHF. To our knowledge, such a scenario has never been reported as a harbinger of NGD in the English literature. We highlight that early diagnosis of NGD can be achieved by clinical manifestations of tachycardia, tachypnea, and systemic hypertension, laboratory data of hyperthyroidism, a maternal history of unquenched or refractory hyperthyroidism of GD, and elevations of TSI in the mother and the baby. The pathogenesis of PPHN, MI, SVT, and CHF in NGD will be briefly discussed.

CASE

A 12-day-old baby boy was referred from a part-time pediatrician in an obstetric clinic with the chief complaints of tachycardia (> 200/min), tachypnea (> 60/min), and systemic hypertension (with systolic pressure > 90 mmHg). He was born of a gravida 1 and para 1 34-year-old mother at gestation age of 37^{+5} weeks via Caesarean section due to deceleration of fetal heart beats. At referral to the outpatient clinic, jitteriness or hyper-excitability was discernible on physical examination. His eyes were wide-open. There was no exophthalmos and eyelid retraction. On admission at the Pediatric Intensive Care Unit, he was 2,600 gm in weight, and 49 cm in length. Heart rate was 216/min, respiratory rate 70/min, and blood pressure 103/80 mmHg. Chest radiogram showed cardiomegaly, with a cardiothoracic ratio of 60%. Echocardiography with Doppler showed a shortened pulmonary acceleration time (40 ms). Mean pulmonary arterial pressure was 60 mmHg, indicating presence of PPHN. SVT, with a heart rate of 220/min, was noted on the electrocardiographic monitoring. Potassium level was 5.5 mmol/L (> 4.5 mmol/L). Cardiac troponin-I was 0.16 ng/mL (> 0.03 ng/mL), myocardial fraction of creatine kinase (CK-MB) mass 8.5 ng/mL (> 0.6-6.3 ng/mL), and N-terminal pro-brain natriuretic peptide (NT pro-BNP)

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11,091 pg/mL (> 450 pg/mL), indicating presence of MI and CHF. Renin was 26.0 pg/mL (> 3.6 pg/mL-20.1 pg/mL). Thyroid stimulating hormone (TSH) was < 0.01 μIU/mL (< 0.34-5.60 μIU/mL), total thyroxine (T4) 23.53 μg/dL (> 6.09-12.23 μg/dL), free T4 5.69 ng/dL (> 0.61-1.12 ng/dL), free triiodothyronine 4.85 ng/mL (> 0.87-1.78 ng/mL), and anti-TSH receptor antibody 32.54 IU/L (> 1.75 IU/L; cutoff value for GD). Thyroid sonography showed increased vascularity. Maternal GD was confirmed by the clinical feature of residual exophthalmos, a history of subtotal thyroidectomy, and hyperthyroid function in the third trimester. She had been treated initially with oral methimazole (5 mg, 2 tablets, QD), propylthiouracil (PTU, 50 mg, 1.5 tablets, BID), propranolol (10 mg, 2 tablets, BID), and prednisolone (5 mg, 2 tablets, QD), and then undergone subtotal thyroidectomy for refractory hyperthyroidism 19 months before Caesarean section for this baby boy. PTU (50 mg, 2 tablets, BID) was used in the third trimester. Maternal anti-TSH receptor antibody was 59.85 IU/L (> 1.75 IU/L), indicating that NGD in this baby boy was related to transplacental passage of anti-TSH receptor antibody from the mother. Under the impression of NGD presenting with hyperthyroidism, PPHN, MI, SVT, and CHF, he was treated immediately with oral methimazole (5 mg, 0.25 tablet, QD), oral propranolol (10 mg, 0.25 tablet, QD), oral furosemide (1 mg/kg/day), intravenous milrinone (0.5 μg/kg/min), and nasal continuous positive airway pressure (CPAP) with oxygenation. Inhalation of nitric oxide (NO) was waived, since PPHN was not refractory to the aforementioned treatment options. He was gradually free of cardiopulmonary distress on the 17th day of life, and discharged on the 19th day of life. At the 12-month follow-up, he was 10 kg in weight. Electrocardiogram showed normal sinus rhythm. Echocardiography with Doppler showed regression of PPHN. The ebb and flow of the serum levels of NT pro-BNP, CK-MB mass, troponin-I, anti-TSH receptor antibody, TSH, and free T4, during hospitalization and in the follow-up, was summarized in Figure 1.

DISCUSSION

There were anecdotal reports of NGD individually

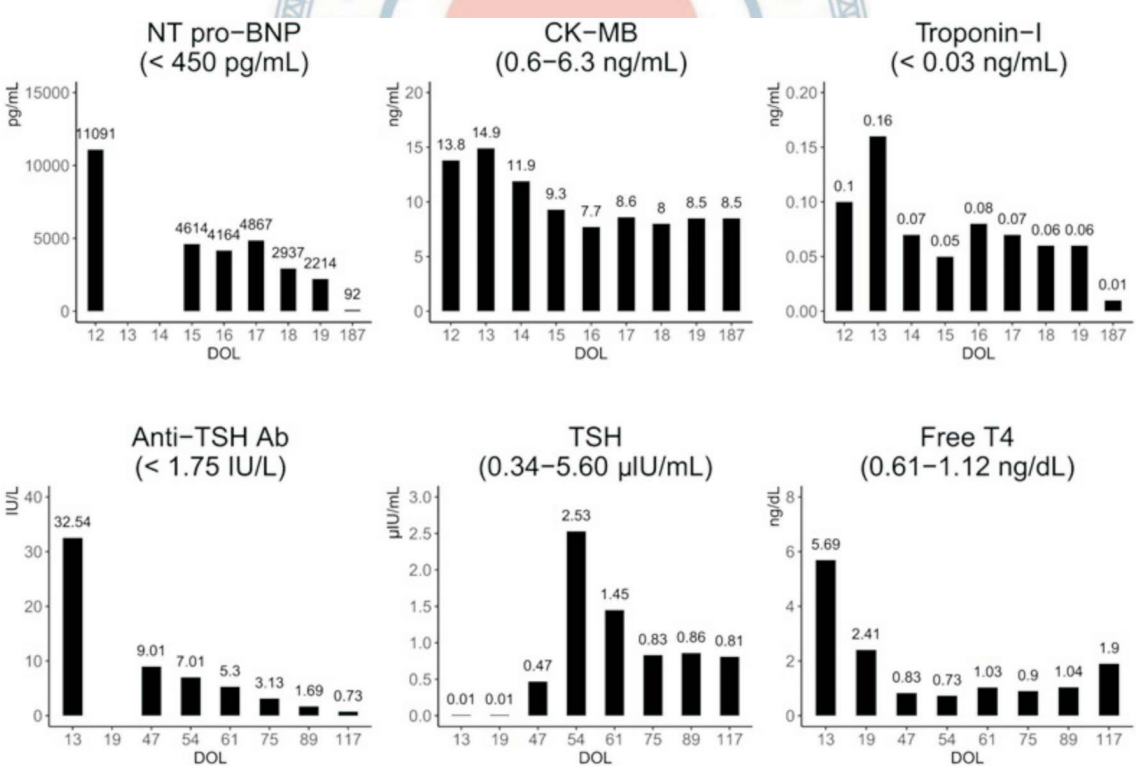

Figure 1. *The ebb and flow of serum levels of NT pro-BNP, CK-MB, troponin-I, anti-TSH Ab, TSH, and free T4 along with the treatment course and the follow-up were marked by day of life. Normal ranges of all six parameters were expressed in parentheses. Ab, antibody; CK-MB, myocardial fraction of creatine kinase; DOL, day of life; NT pro-BNP, N-terminal pro-brain natriuretic peptide; TSH, thyroid stimulating hormone; T4, thyroxine.*

complicated with PPHN,[2-5] MI,[6] and SVT.[7] However, a flagrant combination of PPHN, MI, SVT, and CHF has never been reported simultaneously in NGD. Up to now, there were only five cases of NGD reported to incur PPHN, including the present case (Table 1). All five neonates survived after restoration of euthyroidism and regression of PPHN. The clinical symptoms and signs and treatment options in these five neonates were summarized in Table 1.

The cynosure of this case report is concurrence of PPHN, MI, SVT, and CHF as a harbinger of NGD, which scenario may as well shed light on the pathogenesis of PPHN, MI, SVT, and CHF in NGD.

It is a given that T4 may increase metabolic demands, elevate cytokines, promote chronic hypoxia in the fetuses, and predispose the hyperthyroid fetuses to incur PPHN.[2] In addition, elevated TSI may decrease surfactant production by inhibiting thyroid transcription factor-1, a potent activator of pulmonary epithelial differentiation and surfactant production.[2] In short, T4 has direct and indirect adverse effects on the pulmonary vascular beds in neonates, including alterations in the growth and development of the pulmonary vascular cells, changes in pulmonary vascular dynamics, increased catabolism of endogenous NO, and decreased surfactant production,[2] which may predispose these neonates to incur PPHN. It is beneficial using milrinone to treat NGD which is complicated simultaneously with PPHN, MI, SVT, and CHF, in that milrinone can inhibit phosphodiesterase III in the smooth muscle cells and cardiac myocytes, render vasodilation of the pulmonary vascular beds, and offer inotropy to the myocardium. Amiodarone is contraindicated in treating SVT in NGD,[7] for its similar structure to T4 and high iodine content will contribute to hyperthyroid side effect.

Enhanced sympathetic nervous system and renin-angiotensin system (RAS) have been implicated in the cardiovascular alternations, including myocardial hypertrophy, ischemia, infarction, necrosis, and fibrosis, tachycardia, systemic hypertension, and heart failure, in the human and experimental models with hyperthyroidism.[8] There is a crosstalk between thyroid hormones and the RAS, through modulation of thyroid hormones on the circulating RAS and interaction between thyroid hormones and the cardiac and vascular RAS, after which angiotensin II binds to two selective receptors (angiotensin II type 1 receptor: AT_1-R and angiotensin II type 2 receptor: AT_2-R), exerts angiogenesis via AT_1-R and cellular apoptosis and anti-proliferation via AT_2-R in the human cardiomyocytes and micrcirculation.[8] Tachycardia, systemic hypertension, and left ventricular dysfunction could be induced by excessive L-thyroxin in male Wistar rats, with decreased expression of cardiac AT_1-R and decreased capillary density (cardiac microvascular rarefaction) in the left ventricle, and the so-called cardiac microvascular rarefaction seen in these hyperthyroid rats

Table 1. Neonatal Graves' disease presenting with persistent pulmonary hypertension of the newborn

Patients	Clinical symptoms and signs	Treatment modality	Authors
1/1d/NM	Tachypnea, right-sided pneumothorax, hypoxia, tachycardia, enlarged thyroid gland, exophthalmos	Chest tube, PTU, Lugol's solution, IV hydrocortisone and dopamine, ventilation, oxygen, NOi, IV esmolol, ECMO	Oden[2]
2/9d/M	Tachypnea, tachycardia, hypoxia, jitteriness, diarrhea, a small goiter	Ventilation, oxygen, NOi, IV dopamine/dobutamine, methimazole, Lugol's solution, IV esmolol and hydrocortisone	Obeid[3]
3/6d/M	Meconium stain, grunting, flaring, retraction, tachypnea, left-sided pneumothorax, tachycardia, jitteriness, diarrhea, dehydration, irritability hyperexcitability	Nasal CPAP, oxygenation, needle thoracentesis, chest tube, PTU, propranolol	Markham[4]
4/9d/M	Vomiting, diarrhea, tachypnea, sweating, apnea, bradycardia, hypoxia, tachycardia, goiter	Digoxin, lasix, fluid restriction, ventilation, oxygenation, propranolol, Lugol's solution	O'Donovan[5]
5/12d/M	Tachypnea, tachycardia, systemic hypertension	Nasal CPAP, oxygenation, methimazole, propranolol, lasix, IV milrinone	Lee[11]

CPAP, continuous positive airway pressure; d, day; ECMO, extracorporeal membranous oxygenation; IV, intravenous; M, male; NM, not mentioned (gender); NOi, inhalation of nitric oxide; PTU, propylthiouracil.

could be reversed by chronic treatment of losartan (an AT_1-R blocker), diltiazem (a calcium channel blocker), and propranolol (a beta-adrenergic blocker).[9] A substantial number of hypothesis have been proposed to decipher the genesis of myocardial injury due to coronary microvascular dysfunction, which include dysfunction of endothelial cells, dysfunction of smooth muscle cells, microvascular spasm, sympathetic dysfunction, altered microvascular remodeling, vascular rarefaction, among others.[10]

In conclusion, tachycardia, tachypnea, and systemic hypertension in the neonate(s) born of mother(s) with unquenched hyperthyroidism of GD should raise our suspicion of such life-threatening complications of PPHN, MI, SVT, and CHF in NGD, which could be curable after restoration of euthyroidism.

LEARNING POINTS

- The cynosure of this case is concurrence of PPHN, MI, SVT, and CHF as a harbinger of NGD, which scenario has never been reported in the English literature and may shed light on the pathogenesis of PPHN, MI, SVT, and CHF in NGD.
- Tachycardia, tachypnea, and systemic hypertension in the neonate(s) born of mother(s) with refractory hyperthyroidism due to GD should raise our suspicion of such life-threatening complications of PPHN, MI, SVT, and CHF in NGD, which could be curable after restoration of euthyroidism.

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CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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