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Case Report

Hepatic Failure Resulting from Neonatal Thyrotoxicosis

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Abstract: The objective was we report a case of jaundice, fulminant hepatic failure and pulmonary hypertension in premature baby caused by neonatal thyrotoxicosis. The Methods were We describe the clinical and laboratory findings relating to the case in Results A premature baby boy born to a primigravida mother by cesarean section was born by cesarean section at 31 weeks of gestation because of fetal tachycardia (heart rate: 190 beats/min). At birth, the patient presented with tachycardia (heart rate: 220–240 beats/min), respiratory distress, hepatomegaly and jaundice. The mother had mild exophthalmos and had undergone radio ablation for Graves' disease 6 years prior to conception. The neonate was diagnosed as having neonatal thyrotoxicosis causing pulmonary hypertension and hepatic failure. The clinical condition of the neonate improved after treatment was initiated with carbimazole (1.5 mg/kg/day) and propranolol (2 mg/kg/day). The Conclusions To the best of our knowledge, our case is the first reported case of hepatic failure associated with neonatal thyrotoxicosis. Early recognition and treatment of neonatal thyrotoxicosis are crucial to avoid the associated complications, which include hepatic failure.
Keywords: Premature baby, hepatic failure, neonatal thyrotoxicosis, Graves' disease, thyroid-stimulating immunoglobulins, carbimazole

INTRODUCTION

Thyrotoxicosis can cause hepatic or cholestatic liver injury [1–4]. The exact mechanism is not clear, particularly regarding whether the liver injury results from thyroid status or complications such as cardiac failure, hypoxia, and sepsis. However, it is important to recognize that either thyroid or liver disease can adversely affect the function of the other organ.

Neonatal thyrotoxicosis is a rare but serious disease occurs in approximately 1:25,000 neonates [5]. It depends on the TSHR-Ab concentration in maternal serum, the greater the concentration above 500 percent of the normal values in mother's serum the more likelihood of neonatal hyperthyroidism [6]. This explained the rarity of the disease, which is usually caused by the transplacental passage of thyroid-stimulating immunoglobulins (TSIs) from mothers with Graves' disease or a history of Graves' disease, as TSIs remain in the blood even after treatment with drugs, surgery or radioiodine [7]. TSIs are transferred through the placenta to the fetus, where they bind to thyroid-stimulating hormone (TSH) receptors and stimulate thyroid hormone secretion, which can lead to spontaneous abortion, stillbirth, intrauterine growth restriction, fetal goiter and fetal tachycardia [8]. If fetal thyrotoxicosis is not recognized and the fetus is born alive, neonatal thyrotoxicosis requires immediate intervention, as it has a mortality rate of 12–20%, usually from cardiac failure, sepsis or self-limiting hepatitis [9, 10]. We present a rare case that, to the best of our knowledge, is the first case of neonatal thyrotoxicosis with hepatic failure.

CLINICAL CASE A

A premature baby boy born to a primigravida mother by cesarean section at 31 weeks of gestation because of fetal tachycardia, his heart rate was 190 beats/min. Ultrasonography at 28 weeks of gestation had shown intrauterine growth restriction, but no goiter was present. At birth, the neonate weighed 1.5kg and had a pulse of 190–230 beats/min; he was admitted to the intensive care unit, connected to mechanical ventilation, started on antibiotics and treated with surfactant because of respiratory distress. No exophthalmos or goiter was noted, but the loss of

subcutaneous fat was evident. On day 3 of age baby became jaundice with hepatomegaly.

The diagnosis of acute liver failure was considered in view of rapid deranged of liver enzymes, aspartate aminotransferase and alanine aminotransferase (AST and ALT),elevated levels of alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), direct bilirubin, decreased albumin and evidence of coagulopathy (Table1).Altered sensorium was difficult to assess in a baby under sedation and connected to mechanical ventilation. A chest radiograph showed significant cardiomegaly, and echocardiography showed severe tricuspid regurgitation with pulmonary hypertension. The neonate was hypoxic on the high ventilation setting and eventually required high-frequency ventilation and nitric oxide.

Table 1: Values of hepatic indices

	ALP (U/L)	AST (U/L)	ALT (U/L)	Direct Bilirubin (mg/dL)	INR	Albumin (g/dL)	GGT (U/L)
Before treatment	592(54-369)	750(5-34)	117(0–55)	21.8(<15.0)	1.82(0.01-1.24)	2.17(3.8–5.5)	96(12-64)
Five days After treatment	535	392	104	17.9	1.41	2.13	84
Fourteen days after treatment	402	248	77	8.38	1.12	3	62

At 5 days after birth, we noticed mild exophthalmos of the mother's eyes, and when we asked her directly about thyroid disease, she reported that she had undergone radio ablation for Graves' disease 6 years before conception. As a consequence, thyroid function testing of the neonate and TSIs were undertaken (Table2) and Neonatal thyrotoxicosis was diagnosed.

Table 2: Values of thyroid indices

	TSH(μIU/mL)	FT4 (pmol/L)	TSIs
Before treatment	0.0002 (0.35-4.94)	77.22 (9-19)	367 (<140)
Five days After treatment	0.0025	12.09	Not done
Fourteen days after treatment	0.458	14.05	190

The neonate was therefore treated with propranolol (2 mg/kg/day) and carbimazole (1.5 mg/kg/day). Within the next 3 days, the tachycardia resolved, and the neonate was gradually weaned off ventilatory support and extubated. Blood biochemical analysis 5 and 14 days after starting carbimazole revealed improvement of thyroid and liver function (Table1, 2) and jaundice resolved on day 7 of treatment. Repeated echocardiography at 14 days of age showed resolution of pulmonary hypertension.

DISCUSSION

Fetal thyrotoxicosis requires a high index of suspicion to diagnose for different facts first, the disease is rare, second, goiter not always present or can be detected by ultrasound, third fetal tachycardia and growth retardation usually attributed to more common maternal and placental causes than fetal thyrotoxicosis. A maternal history of active or treated Graves' disease is the key clue; however, if this indicator is missed, as it was in our case, fetal tachycardia, fetal growth restriction and fetal goiter on ultrasound are other important clues that necessitate reviewing maternal clinical history and asking the mother direct questions about thyroid disease and related treatments. In this case delay diagnosis attributed to mother's history of Graves' disease and treatment was not provide to physician by mother who was thinking that her Graves' disease is treated already and it will not affect her current pregnancy, and the mild exophthalmos that the mother had been either not appreciated by her physician or was not present during pregnancy. A positive maternal history of thyroid disease should increase suspicion regarding fetal thyrotoxicosis, and the mother's blood should be analyzed for TSIs. If the result is positive and there are clinical signs of fetal thyrotoxicosis, treatment should be started immediately by giving the mother carbimazole or propyl thiouracil, which cross the placenta to the fetus and control fetal thyrotoxicosis [11, 12]. The doses of these drugs are titrated based on fetal heart rate, and if the mother develops treatment-induced hypothyroidism, levothyroxine can be added. The fetal response to treatment is indicated by fetal heart rate control, weight improvement and, if present, goiter shrinkage.

In our case, fetal thyrotoxicosis was not diagnosed in utero and the neonate presented at birth with growth restriction and tachycardia. Signs of thyrotoxicosis in the neonate, such as exophthalmos and

goiter, were not present. Moreover, jaundice and fulminant hepatic failure only became apparent on the third day after the neonate was born. Mild exophthalmos in the mother, which we noticed at 5 days after the birth, raised the possibility of neonatal thyrotoxicosis, which was confirmed by high FT4 levels and low TSH levels.

Mild hepatic injury with hyperthyroidism is not uncommon in adult thyrotoxicosis [13-15]. However, adult hepatic failure as a result of thyrotoxicosis is rare only few case reports in the literature [16], first reported by Habershon in 1874 [17]. To the best of our knowledge, our case is the first reported case of hepatic failure caused by neonatal thyrotoxicosis.

The hepatic injury that is caused by hyperthyroidism varies from an increase in hepatic enzymes, as reported in most cases [1-3], to severe hepatic failure [16]. The most plausible explanation for the development of hepatic failure in patients with hyperthyroidism is central hepatic ischemia due to increased hepatic oxygen demand and decreased hepatic blood flow caused by hyperthyroidism and heart failure [18, 19]. Hepatic pathological changes in patients with thyrotoxicosis range from focal necrosis with fatty changes to cirrhosis [20]. The research related to this topic in children and neonates is lacking. Antithyroid therapy for patients with liver disease must be cautiously initiated, as the therapy itself may cause hepatic dysfunction [21]. However, we chose carbimazole because of the problems with propyl thiouracil including fatal cases of hepatitis [22-23]. Pulmonary hypertension associated with neonatal thyrotoxicosis is rare, but it has been previously reported [24]. The hepatic failure and pulmonary hypertension associated with neonatal thyrotoxicosis in the current case reflect the importance of thyroid hormones for normal body function and the diagnosis of neonatal thyrotoxicosis requires a high index of suspicion.

We conclude that this diagnosis should be considered if the euthyroid mother has a history of treated Graves' disease, if a fetus has unexplained tachycardia with growth restriction, or if a neonate has pulmonary hypertension or hepatic disorders.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Consent

Written informed consent was obtained from the parents of the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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