

# Neonatal Graves' Disease and Cholestatic Jaundice: Case Series and Review of the Literature

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## Abstract

Cholestatic jaundice and elevated liver enzymes are uncommon, but recognized, manifestations of neonatal thyrotoxicosis. Current guidelines for evaluation of cholestatic jaundice and reviews in Neonatology literature do not discuss hyperthyroidism in the differential diagnosis of cholestatic jaundice. We report two cases of neonatal thyrotoxicosis secondary to neonatal Graves' disease that presented with cholestatic jaundice and elevated liver enzymes at birth. Early recognition of thyrotoxicosis as a cause of the hepatic disease in the neonate is crucial to prevent unnecessary diagnostic procedures and to initiate timely treatment.

## Keywords

Neonate, Graves' Disease, Thyrotoxicosis, Hyperthyroidism, Cholestasis, Hepatitis, Jaundice, Conjugated Hyperbilirubinemia

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## 1. Introduction

Cholestatic jaundice and elevated liver enzymes are uncommon, but recognized, manifestations of neonatal thyrotoxicosis. We report two neonates with cholestasis associated with neonatal thyrotoxicosis caused by maternal Graves' disease. The cause of liver disease in neonatal thyrotoxicosis has not been clearly established. Early recognition of thyrotoxicosis as a cause of the hepatic disease in the neonate is crucial to prevent unnecessary diagnostic procedures and to initiate timely treatment.

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## 2. Case 1

A 1285 g (50% percentile) female infant born by cesarean section at 29 weeks gestation to a 36-year-old mother, gravida 2 para 1, due to premature labor. The mother had a history of hypothyroidism and was treated with thyroid hormone replacement throughout the pregnancy.

Vital signs were within normal at birth except for tachypnea with a respiratory rate of 60 - 70/minute. The infant had respiratory distress secondary to hyaline membrane disease which required surfactant therapy and ventilator support for four days. Initial exam revealed jaundice and a diffuse rash with petichiae and macules distributed over the entire body but sparing palms and soles. Hepatosplenomegaly was present (liver 3.5 cm below costal margin, spleen 4 cm below costal margin). Facies were triangular with frontal bossing and both eyes were prominent with yellow sclera. A II/VI systolic murmur was noted.

Laboratory studies on the first day of life revealed thrombocytopenia with platelet count of 64,000/L, conjugated hyperbilirubinemia with a total bilirubin of 10.7 mg/dl and a direct of 7.8 mg/dl, and elevated liver enzymes with AST of 586 U/L (18 - 74), and ALT of 177 U/L (8 - 36). Based on the clinical picture, congenital infection was suspected and studies for toxoplasma, rubella, cytomegalovirus and herpes (TORCH) were performed and were normal. On day 2 of life, an echocardiogram revealed significant pulmonary hypertension with bidirectional shunt through a patent ductus arteriosus. Cranial ultrasound showed borderline enlargement of the lateral ventricles with no intracranial calcification or bleeding.

On day 4, the infant was extubated to CPAP but remained tachycardic with a heart rate of 180 - 200/minute and worsening of tachypnea with respiratory rate of 70 - 80/minute was noted. Nitric oxide (NO) was started for persistent pulmonary hypertension. NO was continued for 3 days and the pulmonary blood pressure normalized thereafter. Thrombocytopenia persisted and the conjugated hyperbilirubinemia continued to increase to a peak of 20.3 mg/dl total and 11.5 mg/dl conjugated on day 8 of life. Liver enzymes remained elevated and peaked on day 11 with AST of 771 U/L and ALT of 364 U/L. Abdominal ultrasound confirmed hepatosplenomegaly without a discrete mass lesion and no intrahepatic or extrahepatic biliary tree obstruction. Studies to evaluate the etiology of cholestatic jaundice including alpha-1-antitrypsin deficiency, tyrosinemia, and galactosemia were performed and were normal.

On day 11, mild exophthalmos of the mother was noted and further questioning revealed that she was diagnosed with Graves' disease 8 years previously and treated with radioactive iodine therapy resulting in hypothyroidism. Based on this history thyroid profile was obtained on the infant and revealed elevated T4 at 25.3 ug/dl (normal range 9.8 - 16.6) and suppressed TSH 0.011 uIU/ml (normal range 0.4 - 8.6). Antibody mediated Neonatal Grave' disease was confirmed by presence of TSH receptor antibodies which were significantly elevated at 302% (normal 0% - 129%). Careful examination of the infant revealed diffuse goiter. Treatment was initiated with methimazole on day 12 and resulted in gradual improvement of the thyroid profile as well as the conjugated bilirubinemia and liver function tests (**Table 1**). Treatment with methimazole continued for 2 months. A slight increase in AST and ALT was noted one month after Methimazole discontinuation but then gradually improved thereafter.

## 3. Case 2

An 1820 gm (75<sup>th</sup> percentile) male infant born by cesarean section at 32 weeks gestation to a 35-year-old mother, gravida 2 para 1, with a history of hypothyroidism treated with thyroid hormone replacement therapy.

Initial physical exam was remarkable for triangular facies, penoscrotal hypospadias, hepatosplenomegaly and jaundice. Vital signs were significant for tachypnea at birth with a respiratory rate of 50 - 60/minute. The baby required ventilatory support for 6 days by CPAP.

Laboratory studies on the first day of life revealed thrombocytopenia with platelets of 75,000/L, conjugated hyperbilirubinemia with a total bilirubin of 8.3 mg/dl and a direct bilirubin of 4.4mg/dl. On day 2, elevated liver enzymes were noted with ALT of 67 U/L and AST of 116 U/L. Cranial ultrasound showed mild lateral ventricular enlargement with no calcification or bleeding. Echocardiogram revealed mild pulmonary hypertension with tricuspid regurgitation and increased right ventricular pressure. Evaluation for congenital infection (toxoplasma, rubella, syphilis, CMV, and HSV), viral hepatitis, alpha-1-antitrypsin deficiency and tyrosinemia were normal.

Endocrinology evaluation was performed to evaluate the pituitary function as part of the diagnostic workup for penoscrotal hypospadias revealed neonatal hyperthyroidism. On day 6 of life, Total T3 was 688 ng/dl (normal range 0 - 256), free T4 > 12 ng/dl (normal range 1.71 - 6.6), total T4 28 ug/dl (normal range 10.1 - 20) and TSH was suppressed 0.006 uIU/ml (normal range 0.4 - 8.6). Antibody mediated neonatal Graves' disease was

confirmed by presence of elevated TSH receptor antibodies at 49% (normal 0% - 14%). Additional history elicited after identification of neonatal Graves' disease revealed maternal history of Graves' disease treated with radioactive iodine 5 years prior to this pregnancy with resultant hypothyroidism. The infant was started on propylthiouracil (PTU) and propranolol.

Thyroid profile improved within 48 hrs to T3 of 371 ng/dl, free T4 of 5.58 ng/dl, and total T4 of 22.3 ug/dl. Thyroid hormone levels normalized by 3 weeks of age (**Table 2**). The conjugated hyperbilirubinemia peaked on day 12 of life with a total bilirubin of 10.2 mg/dl and a direct of 6.2mg/dl and gradually improved with normalization by 8 weeks. Liver enzymes transiently increased after initiation of PTU treatment and peaked on day 12 of life (6 days on PTU treatment) with ALT 137 U/L and AST 230 U/L. Thereafter, there was gradual improvement in the ALT and AST with normalization by 8 months (**Table 2**).

**Table 1.** Case 1 laboratory studies.

Day of Life	AST (U/L)	ALT (U/L)	Bilirubin Total (mg/dl)	Bilirubin Direct (mg/dl)	Platelet $\times 10^3$ /ul	Total T4 (ug/dl)	TSH (uIU/ml)
1	586	177	10.7	7.8	64	-	-
3	342	197	15.9	9.8	98	-	-
8	405	234	20.7	12.1	84	-	-
11	771	364	15.4	9.0	60	25.3	0.011
20	430	199	10.6	6.3	76	13.1	0.014
30	369	237	9.4	5.8	169	9.9	0.012
40	220	145	5.8	3.7	187	3.7	0.012
60	301	273	-	-	-	7.6	0.223
120	195	299	2.0	1.3	-	9.7	0.89
200	89	145	0.3	0.12	-	6.4	0.59
230	71	138	0.3	0.08	-	-	-
Normal	(18 - 74)	(8 - 36)	0 - 3 d (2 - 10) >1 mo (0 - 1.5)	0 - 3d < 1.5 >1mo < 0.5	(250 - 450)	1 - 7 d (10.1 - 20) 8 - 14 d (9.8 - 16.6) 1 mo - 1y (5.5 - 16)	(0.4 - 8.6)

AST: Aspartate Amino-Transferase; ALT: Alanine Amino-Transferase, T4: Thyroxine; TSH: Thyroid Stimulating Hormone.

**Table 2.** Case 2 laboratory studies.

Day of Life	AST (U/L)	ALT (U/L)	Bilirubin Total (mg/dl)	Bilirubin Direct (mg/dl)	Platelet $\times 10^3$ /ul	Total T4 (ug/dl)	TSH (uIU/ml)
1-2	116	67	8.3	4.1	75	-	-
6	105	74	8.5	5.6	136	28	0.006
12	230	137	10.2	6.2	302	20	0.007
20	132	85	6.9	4.6	318	11	0.004
30	121	119	7.0	4.7	297	9.9	0.010
60	75	105	1.0	0.4	-	-	0.014
120	60	75	0.6	-	265	10.8	0.275
240	57	22	-	-	323	8.6	0.413
Normal (18 - 74)	(18 - 74)	(8 - 36)	0 - 3 d (2 - 10) >1 mo (0 - 1.5)	0 - 3 d < 1.5 >1 mo < 0.5	(250 - 450)	1 - 7 d (10.1 - 20) 8 - 14 d (9.8 - 16.6) 1 mo - 1 y (5.5 - 16)	(0.4 - 8.6)

## 4. Discussion

Neonatal Graves' disease affects 1% - 2% of infants born to mothers with a history of Graves' disease [1] [2]. The disease results from the transplacental passage of maternal Thyroid Stimulating Hormone Receptor Antibodies (TSHR-AB) [2]-[4]. While most infants are born to women with active Graves' hyperthyroidism, the disorder can also occur in infants of women with a history of Graves' hyperthyroidism treated with thyroidectomy or radioactive iodine in the past [5]. Our cases emphasize the importance of a thorough history in mothers who are on thyroid hormone replacement therapy during pregnancy to elucidate the etiology of the hypothyroidism. Recognition of the infants risk for neonatal Graves' is crucial for early diagnosis and treatment. Measurement of maternal serum TSHR-Ab is also helpful in predicting whether a newborn will be affected [6].

Neonatal Graves' disease has been reported to cause low birth weight for gestational age, premature birth, microcephaly, frontal bossing and triangular facies, warm, moist skin, irritability and hyperactivity [7] [8]. Tachycardia with a bounding pulse, pulmonary hypertension, high-output heart failure, fetal hydrops, hyperphagia, poor weight gain and diarrhea may also be present [8]. Thrombocytopenia, hepatosplenomegaly, jaundice, diffuse goiter, stare and occasionally exophthalmos may be evident [9]. Untreated neonatal hyperthyroidism has a high mortality rate and serious neurologic sequelae [10].

The time of onset is variable, depending upon whether the mother is receiving an antithyroid drug at the time of delivery and the presence of TSH receptor blocking antibodies. Infants of mothers taking an antithyroid drug may be euthyroid at birth, and become hyperthyroid several days later, as the antithyroid drug is metabolized or excreted [11]. The presence of blocking antibodies may delay the onset of clinical hyperthyroidism by weeks or months. The symptoms usually resolve spontaneously by 3 to 12 weeks as the maternal TSHR-Ab disappears from the infant's circulation. By 4 months of age, most infant are euthyroid and off antithyroid medication treatment [8] [9].

Hepatic manifestations of Graves' disease are recognized in both adults and neonates [12] [13]. The pathology of liver disease associated with hyperthyroidism was first reported in adults in the 1930s [13]. In a 1992 review of adults with hyperthyroidism in the *Journal of Clinical Gastroenterology*, the subset of patients without congestive heart failure presented with hepatosplenomegaly in 1/3 and cholestatic jaundice in 1/2 of the patients [13]. Two thirds of the patients had elevated liver enzymes, but only 5% of these had liver enzymes over 250 U/L.

Our two patients with neonatal hyperthyroidism presented with hepatosplenomegaly, conjugated hyperbilirubinemia and elevated liver enzymes. Hepatic manifestations of neonatal hyperthyroidism were reported as early as 1955 and are recognized, though less common, manifestations of neonatal Graves' disease [14]. Literature review identified 11 case reports discussing the hepatic manifestations of neonatal Graves' disease [14]-[24]. The majority had hepatosplenomegaly and early cholestatic jaundice presenting at birth or in the first week of life. Approximately half reported elevated liver enzymes with AST generally higher than ALT as was evident in our patients. The highest levels reported were AST 1111 U/L [24] and ALT 465 U/L [17]. Very limited information is available about the time course of recovery. In our patients, the time course to complete recovery was 6 - 9 months with the improvement in AST and ALT lagging behind resolution of conjugated hyperbilirubinemia.

Conjugated hyperbilirubinemia is estimated to occur in 1 of 2500 live birth [25]. The differential diagnosis of conjugated hyperbilirubinemia is extensive, but most affected infants present with progressive and prolonged jaundice. The early cholestasis seen in our patients was also evident in the cases reported in the literature and may also be seen in patients with congenital infection and embryonic biliary atresia. Despite the recognition of the hepatic manifestations of hyperthyroidism in the literature, this complication of neonatal Graves' disease is not listed in the differential diagnosis of cholestatic jaundice in recent guidelines for evaluation of cholestatic jaundice [25]-[27]. This lack of recognition may result in a delay in diagnosis and appropriate therapy or lead to unnecessary diagnostic procedures.

The cause of liver disease in neonatal thyrotoxicosis has not been clearly established but several possibilities have been suggested. The hypermetabolic state may result in increase hepatic oxygen consumption without increased hepatic blood flow, leading to hepatic dysfunction [28] [29]. Another possibility is that thyrotoxicosis causes high output congestive heart failure (CHF), which may result in hepatic dysfunction and hepatosplenomegaly [30]. However, in both the adult and pediatric literature, the hepatic manifestations occur in hyperthyroid patients without CHF [13]. Propylthiouracil (PTU) induced hepatitis is another possible mechanism [30] [31]. In three reported cases the fetus was exposed to PTU, however, these infants had a mild elevation in liver en-

zymes compared to the elevation reported in unexposed cases, including our two patients who were not exposed to PTU. Enlargement of the reticuloendothelial system seen in neonatal Graves' disease may disrupt hepatic architecture and cause cholestasis [32].

## 5. Conclusion

In summary, neonatal Graves' disease is a rare, but potentially fatal, condition. Cholestatic jaundice with hepatosplenomegaly and hepatitis are unusual, but recognized, complications of neonatal Graves' disease. Identification of an affected infant requires a careful maternal history, a high index of suspicion and an improved recognition of neonatal Graves' disease in the differential diagnosis of cholestasis.

## Conflict of Interest

The authors of this manuscript report no conflicts of interest including, but not limited to, consulting fees, paid expert testimony, employment, grants, honoraria, patents, royalties, stocks, or other financial or material gain that may involve the subject matter of the manuscript.

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