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Case Report

Paediatrics Section

# Neonatal Hyperthyroidism with Fulminant Liver Failure: A Case Report

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## ABSTRACT

Neonatal hyperthyroidism is a rare disease that is seen in infants born to mothers with Graves' disease. Hepatic manifestation of neonatal hyperthyroidism is extremely rare. We describe a neonate with fulminant liver failure secondary to neonatal hyperthyroidism caused by maternal Graves's disease. The baby was admitted with low birth weight and hepatosplenomegaly. At day 2 of life, the baby was irritable and he developed respiratory distress and fulminant hepatic failure which required mechanical ventilation. All investigations of obstructive, infectious and metabolic causes of hepatic failure were negative. His hepatic dysfunction improvement was correlated with initiation carbimazole as anti-thyroid medication. The conjugated hyperbilirubinemia, liver enzymes and International Normalised Ratio (INR) were gradually improved with normalization by eight weeks. This case has been reported to illustrate lessons learnt for early identification of neonate with hyperthyroidism as potential cause of cholestasis is important, because delayed treatment of hyperthyroidism might lead to irreversible consequences such as mental retardation or even death due to liver failure.

**Keywords:** Cholestasis, Graves' disease, Liver diseases

## CASE REPORT

A male infant was delivered at 36th week gestational age with a birth weight of 1.9 kilogram via spontaneous vaginal delivery to a 29-year-old primiparous woman.

The mother had late antenatal booking and was suspected to have Graves' disease at third trimester of pregnancy. Thyroid function test confirmed maternal thyrotoxicosis {free T4: 97 (9 to 26 pmol/L), TSH: 01 (0.5 to 5.0 mU/l), TSI: 308 (<140 mg/dl)} and she was prescribed propyl-thiouracil for two weeks until delivery. There was no previous history of abortion and no family history of liver diseases.

The infant was admitted into neonatal intensive care unit with low birth weight and hepatosplenomegaly. On examination, he was tachycardiac and his conjunctiva was icteric. No jitteriness or sweating was observed. There was no goiter, eye lid retraction or proptosis. Other systemic examinations were normal. At day 2 of life, the baby was irritable and he developed respiratory distress which required mechanical ventilation because of pulmonary hypertension.

The laboratory analysis revealed thrombocytopenia, coagulopathy and abnormal liver biochemistry. Investigations are summarized in [Table/Fig-1]. Tests for cytomegalovirus, herpes simplex, Epstein–Barr virus, enteroviruses, adenovirus and parvovirus B19 were negative. Full screening for galactosemia, tyrosinemia, mitochondrial respiratory chain disorders, inborn errors in bile acid synthesis and neonatal hemochromatosis were negative. Abdominal ultrasound confirmed the presence of hepatosplenomegaly but did not suggest extrahepatic biliary obstruction or ascites.

Initial management comprised a platelet transfusion, fresh-frozen plasma, intravenous vitamin K and empirical antibiotic treatment. Ursodeoxycholic acid and fat-soluble vitamin supplements were added. In spite of treatment, his liver function tests were deteriorated with persistent hyperbilirubinaemia, elevated serum transaminase concentrations and severe coagulopathy with INR: 9. The baby was diagnosed with fulminant hepatic failure based on biochemical evidence of acute liver injury (cholestasis and hepatitis) and coagulopathy with INR more than 2.0 not corrected by vitamin K. Thyroid function tests, which were requested on day 6 of life in view of the mother's past medical history, revealed that the infant was suffering from neonatal hyperthyroidism [Table/Fig-1].

The infant was treated with carbimazole as antithyroid medication. The conjugated hyperbilirubinemia, liver enzymes and INR were gradually improved with normalization by eight weeks [Table/Fig-1].

| Test | Result Pre-treatment (2 days of age) | Result Post-treatment (8 weeks of age) | Normal range |
|---|---|---|---|
| Total bilirubin | 298.2 | 17.8 | 2.1-15.5 µmol/l |
| Direct bilirubin | 101 | 8.5 | 0.0-9.0 µmol/l |
| AST | 633 | 52 | 10-55 µ/l |
| ALT | 504 | 45 | 6-50 µ/l |
| Albumin | 31 | 39 | 38-54 g/l |
| ALK | 869 | 429 | 1-500 IU/l |
| GTT | 497 | 65 | 7-30 IU/l |
| INR | 5.8 | 1.1 | 0.8-1.2 |
| Serum glucose | 3.1 | 5.0 | 3.3-5.6 mmol/l |
| Free T4 | >87 | 19 | 9 to 26 pmol/l |
| Total T3 | > 8.36 | 2.5 | 1.2 to 2.6 nmol/l |
| TSH | <0.02 | 0.52 | 0.5 to 5.0 mU/l |
| TSI | 471 | 131 | <140 mg/dl |
| White blood cell | 5.9 | 6.7 | 6-16 × $10^9$/l |
| Haemoglobin | 10.7 | 11.3 | 12. 2-15.3 gm/dl |
| Platelet | 63 | 197 | 150-450 × $10^9$/l |

**[Table/Fig-1]:** The laboratory tests.
ALT: Alanine transaminase, AST: Aspartate aminotransferase, ALK: Alkaline phosphatase, GGT: Gammaglutamyltransferase, INR: International normalized ratio, TSH:Thyroid-stimulating hormone, TSI: Thyroid-stimulatingimmunoglobulins.

## DISCUSSION

Neonatal hyperthyroidism is a rare disease affecting infants of mothers with Graves' disease. It is usually caused by transplacental passage of maternal thyrotropin receptor (TSHR) antibodies, which leads to transient hyperthyroidism in neonate

[1]. Cholestatic jaundice with hepatosplenomegaly and hepatitis are unusual, but recognized, complications of neonatal Graves' disease [2]. This is a report of neonate with hepatic failure associated with hyperthyroidism caused by maternal Graves' disease. Hepatic dysfunction improvement was correlated with initiation of antithyroid treatment. Although, neonatal hyperthyroidism is usually self-limited, it can be severe, even life-threatening condition [3]. Cholestasis is common in neonate and the aetiologies are multifactorial including obstructive, infectious and metabolic causes [4]. Hyperthyroidism is not typically considered a cause of neonatal conjugated hyperbilirubinemia. However, few case reports described the hepatic manifestation of neonatal thyrotoxicosis. Loomba-Albrecht LA et al., reported a neonate with cholestasis associated with hyperthyroidism caused by maternal Graves' disease [5]. Almadhoun et al., reported that cholestatic jaundice with hepatosplenomegaly and hepatitis are complications of neonatal Graves' disease [6]. Other two reports described hyperthyroid infants born to mothers with Graves' disease have developed coagulopathy and conjugated hyperbilirubinemia [7,8]. All previous four reports never described a neonatal liver failure associated with hyperthyroidism caused by maternal Graves's disease. However, our case is consistent with findings from recent case report [9]. The data of the five reports taken together with the observation in our patient suggest that hyperthyroidism be considered a potential aetiology of cholestasis and liver dysfunction in neonates.

The aetiology of neonatal hyperthyroidism-associated cholestasis and liver failure is unknown. One possible mechanism would explain enlargement of the reticuloendothelial system seen in neonatal Graves' disease may disrupt hepatic architecture and cause cholestasis [10]. In animal study Chandra AK et al., demonstrated that thyroxine, perhaps by increasing oxygen consumption increases free radical generation, particularly in liver, thus inducing liver injury in rats [11].

In our patient, we hypothesized the mechanism of liver failure in neonatal hyperthyroidism is that thyrotoxicosis causes high output congestive heart failure which may result in hepatic dysfunction and hepatosplenomegaly [12].

## CONCLUSION

We described a baby boy with hepatic failure associated with hyperthyroidism caused by maternal Graves' disease. His hepatic dysfunction improvement was correlated with initiation of antithyroid treatment. Neonatal hyperthyroidism should be considered in the differential diagnoses of neonatal cholestasis. The early identification of neonate with hyperthyroidism as potential cause of cholestasis is important, because delayed treatment of hyperthyroidism might lead to irreversible consequences such as mental retardation or even death due to liver failure. This case report emphasizes the need for more research to help in understanding the association of liver diseases with neonatal hyperthyroidism.

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