Neonatal Hyperthyroidism Presenting as Neonatal Cholestasis

Abstract
Neonatal cholestasis has varied etiology including both medical and surgical causes. Hypothyroidism is well known treatable cause of cholestasis but hyperthyroidism though rare is a reported cause of cholestasis and is treatable. Our case presented with failure to thrive, features suggestive of cholestasis and hepatospleno-megaly. Further evaluation revealed maternal and neonatal hyperthyroidism. Baby was treated with antithyroid medication, methimazole. Improvement in cholestasis and weight gain was noted with methimazole. Hyperthyroidism albeit rare is an important treatable cause of neonatal cholestasis [1].

Case Highlights
i. Hyperthyroidism though rare is a treatable cause of neonatal cholestasis
ii. Abnormally low TSH values in thyroid screening test should be repeated with T4 levels

Introduction
Cholestasis in the neonates requires extensive and timely evaluation to find out the underlying cause as some require medical and some surgical management. Cholestasis in neonate has varied etiology and one of the rare cause is thyroid dysfunction. Hypothyroidism is a well known cause of cholestasis but the other end of thyroid dysfunction, hyperthyroidism is rare to be associated with cholestasis. Neonatal hyperthyroidism is a transient entity, with a spectrum of manifestations including failure to thrive, fever, craniosynostosis, microcephaly and signs of congestive cardiac failure. Neonatal cholestasis is a rare manifestation with only few reported cases in the literature till date. So we report such a manifestation.

Case Presentation
A one month old male infant born out of non consanguineous marriage was brought with complaints of not gaining weight since birth, progressively increasing yellowish discoloration of eyes and body for 15 days, high colored urine staining the diapers for 10 days but there was no history of pale stools, any evidence of bleeding or abdominal distention, decreased activity and poor feeding. Furthermore there was no history suggestive of excessive cry, irritability, seizures, vomiting, constipation or loose stools. Infant was born to a second gravid mother with previous abortion at four months of gestation. She was a known case of hyperthyroidism and was on carbimazole prior to pregnancy and on propylthiouracil during the pregnancy. No other significant antenatal events were noted. Baby was delivered at term through normal vaginal route, cried immediately after birth and passed meconium on day one of life with birth weight of 2.3 Kg. Baby was admitted on day 2 of life for indirect hyperbilirubinemia and was started on phototherapy. No family history of similar illnesses was noted.

On examination baby was active, icteric, without any pallor, edema, or dysmorphism. Admission weight was 2.02 Kg (<3rd percentile), head circumference - 30cm (< 3rd percentile), length - 48cm (<3rd percentile). Baby’s sleeping heart rate was 160-180/m. Systemic examination revealed hepatomegaly (3cm below costal margin and firm in consistency) and splenomegaly (1cm below costal margin and soft in consistency). No evidence of skin or mucosal bleeds was noted. Infant was active with normal tone and was feeding well at mother’s breast.

Investigations
At the time of admission child had deranged liver function in the form of elevated total serum bilirubin(13.5mg/dl) and direct bilirubin levels (7.5mg/dl), significantly elevated liver enzymes (SGOT-165U/L, SGPT-410U/L, ALP-1420U/L), decreased total protein (4.8gm/dl) and hypoalbuminemia (2.4gm/dl). Thyroid function tests revealed highly elevated total T3 (410.90ng/dl) {(Free T3-11.53pg/ml) and total T4 levels (>24.86µg/dl) [Free T4-7.77ng/dl]} with suppressed TSH levels (0.01µIU/ml). Evaluation of cause of hyperthyroidism revealed highly elevated TSH Receptor antibodies->40IU/L (Reference <1.75IU/L) and other investigations were within normal limits including urine for reducing substances (negative), complete blood picture and CRP. Blood culture was sterile.

Differential Diagnosis considered were
Neonatal hyperthyroidism
• Idiopathic neonatal hepatitis
• Intraterine infection: No history suggestive of TORCH infections in mother and negative panel for intra uterine infections
Neonatal Hyperthyroidism Presenting as Neonatal Cholestasis

- Galactosemia: urine for reducing substance and enzyme levels were normal
- Bacterial sepsis: blood culture was sterile
- Urinary tract infection: urine routine examination was normal and urine culture was sterile
- Extrahepatic biliary atresia: No history of acholic stools and USG abdomen was normal

Infant was started on Methimazole 0.45mg/kg/day in divided doses. Nutritional supplementation of vitamins and minerals were also started as per guidelines for cholestasis.

With antithyroid medication baby improved over the next 2 weeks in form of good weight gain and improved liver function. Repeat Liver functions tests were as follows:

- Total Bilirubin-11.6mg/dl (direct-5.9mg/dl)
- SGOT-171U/L
- SGPT-391U/L
- ALP-1076U/L
- Total Protein-6.0gm/dl
- Albumin-3.4gm/dl

**Discussion**

Neonatal cholestasis has varied etiologies, including anatomic, infectious, and metabolic abnormalities [2]. Usually hyperthyroidism is associated with neonatal cholestasis but rarely hyperthyroidism is also known to be associated with cholestasis. Literature review revealed four cases of neonatal hyperthyroidism presenting with cholestasis. Neonatal Graves disease refers to congenital hyperthyroidism in infants born to mothers with Graves disease. Incidence of Graves’ disease in pregnant women is estimated to be 0.2%. Only 1-2% of infants born to these pregnant women present with fetal and neonatal hyperthyroidism [3,4]. Transplacental transfer of maternal TSHR-Ab (Thyroid Stimulating Hormone Receptor Antibody) plays an important role in occurrence of neonatal Graves disease. Transplacental transfer can also occur in a previously treated mother after thyroid ablation as the TSHR-Ab can persist for a long time. Concentration of TSHR-Ab in the third trimester correlates with the likelihood of developing neonatal Graves’ disease [5].

Neonatal Graves disease is usually a transient condition and resolves spontaneously in 3–12 weeks. Manifestations include preterm births, low birth weight, microcephaly, frontal bossing and triangular facies, warm & moist skin, irritability and hyperactivity. Tachycardia with a bounding pulse, pulmonary hypertension, high output heart failure, fetal hydrops, hyperphagia, poor weight gain and diarrhea may also be seen. Thrombocytopenia, hepatosplenomegaly, jaundice, diffuse goiter and occasionally exophthalmos may be evident. Untreated neonatal hyperthyroidism has a high mortality rate and serious neurologic sequelae.

Our case was a term baby and presented with poor weight gain and cholestatic jaundice with mother being a known case of hyperthyroidism on antithyroid medication both prior to and during pregnancy. Loomba-Albrecht et al reported a preterm infant born to a mother with previous history of Graves disease who underwent radioiodine ablation presenting with cholestatic jaundice, thrombocytopenia, tachycardia and hypertension. Raghu U Varier et al. [7] reported an infant born prematurely at 35.5 weeks of gestation and presented with irritability, mild exophthalmos, tachypnea and jaundice but did not have other clinical manifestations of neonatal Graves’ disease. O. Almadhoun et al. [8] reported 2 cases of neonatal hyperthyroidism presented with cholestatic jaundice. Both of them are preterm infants delivered to mothers with hyperthyroidism on hormone replacement therapy. One infant presented with triangular facies, penoscrotal hypospadias, hepatosplenomegaly and jaundice and the second one presented with jaundice, diffuse rash with petechiae and macules distributed over the entire body but sparing palms and soles, hepatosplenomegaly, triangular facies with frontalbossing and prominent eyes. Compared to previous published cases which describe cases when mother was treated with antithyroid medication, our infant presented with hyperthyroidism and cholestaticis and was born to a mother with partially treated Graves disease.

High TSH values in the newborn screen is considered abnormal but low/ undetectable TSH levels should also be considered as abnormal. In order not to miss any case of hyperthyroidism T4 levels should be estimated after both high and low TSH levels.

**References**