

# Neonatal Cholestasis Caused by Undiagnosed Maternal Graves' Disease

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## Abstract

Neonatal cholestasis results from a variety of etiologies, including anatomic, infectious, and metabolic abnormalities. Hyperthyroidism, in contrast to hypothyroidism, is infrequently associated with neonatal cholestasis. Newborn screening is an important tool to detect newborn metabolic disorders, including thyroid dysfunction. However, one must exercise caution when interpreting these reports; typically only high thyroid stimulating hormone (TSH) levels are flagged as abnormal, while low or undetectable levels may not be. We present a unique case of cholestasis in a hyperthyroid neonate of an untreated, undiagnosed mother with Graves' disease; the infant's metabolic screen was not flagged as abnormal.

## Introduction

Neonatal cholestasis can be due to a variety of etiologies, including anatomic abnormalities, infections, and metabolic diseases. Newborn screening has revolutionized the approach to newborn care and allows early disease detection for treatable conditions.<sup>1</sup> However, careful review is required, as newborn screens may only be flagged as abnormal if laboratory values suggest the specific disease for which it was designed (e.g., a high thyroid stimulating hormone [TSH] in the setting of congenital hypothyroidism). At the time of this case in April 2011, the State of Utah screened for 31 diseases using the dissociation-enhanced lanthanide fluorescent immunoassay (DELFI) system.<sup>2,3</sup> As of July 1, 2009, the Utah Newborn Screening Program used TSH to screen for congenital hypothyroidism. Only if TSH is abnormal is a free thyroxine 4 (FT4) reflexively analyzed.<sup>4</sup> We propose that an undetectable or immeasurable TSH should also trigger follow-up with FT4.

## Case Report

A 2.126-kg male infant born via vaginal delivery at 35.5 weeks gestational age to a G1P1 mother developed jaundice. The pregnancy was complicated by pregnancy-induced hypertension and vaginal bleeding. The infant required nasal-CPAP for 3 days, was transitioned to room air, and discharged on day 10 of life. Physical exam was unremarkable, with pigmented stools and no hepatosplenomegaly.

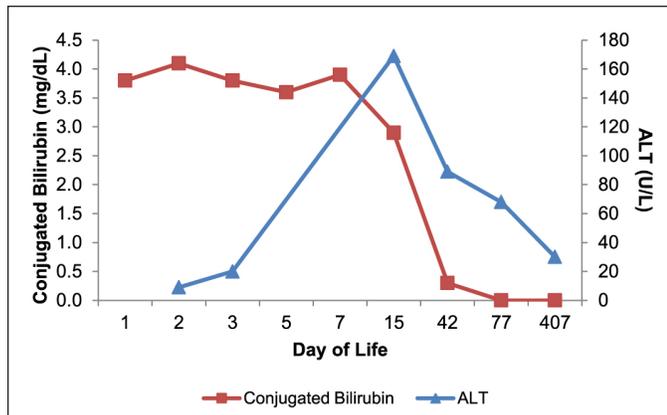
Laboratory evaluation revealed hemoglobin of 21.7 g/dL on day 1 of life and unconjugated bilirubin 6.9 mg/dL on day 2. Peak aspartate aminotransferase (AST) 289 U/L, gamma-glutamyl transferase (GGT) 234 U/L, and prothrombin time (PT) 12.8 seconds were noted on day 15, when he was readmitted to the hospital for respiratory distress. Evaluation for infectious etiologies was negative. Alpha 1-antitrypsin phenotype was MM. He had a normal abdominal ultrasound and echocardiogram. Trends of conjugated bilirubin and alanine aminotransferase (ALT) are shown in Figure 1.

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**Figure 1.** Trend of conjugated bilirubin and ALT over time.

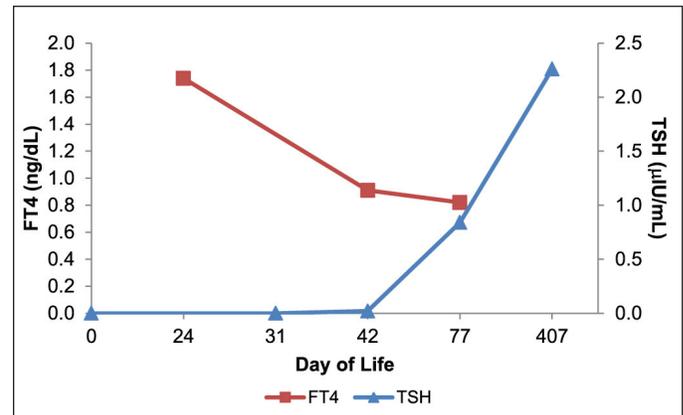
The patient was referred to us at 25 days old. He was vigorous, irritable, growing well, and noted to have jaundice and proptosis. Stools were pigmented and there was no hepatosplenomegaly. At follow-up visit 2 weeks later, proptosis and thyromegaly were appreciated on the patient's mother. Review of the patient's prior laboratory evaluation revealed that though his newborn screen was reported as 'normal,' his TSH level was undetectable. Repeat TSH remained undetectable; however, he had normal FT4, negative TSH receptor (TSHR) antibody (Ab), and negative thyroid stimulating immunoglobulin, confirming the diagnosis of Grave's disease. Treatment was not initiated, given his functional euthyroid state with normal FT4 and negative antibody testing.

At 2.5 months of age, the patient was seen in follow-up with resolved cholestasis, but with continued elevation in transaminases. The most recent follow-up evaluation reveals a normally developing 1-year-old with normal, stable TSH and FT4 levels and normalization of transaminases (Figure 2).

### Discussion

Neonatal cholestasis carries a broad differential diagnosis including obstructive, infectious, and metabolic/genetic etiologies.<sup>5</sup> Hypothyroidism is the most typical thyroid disorder associated with neonatal cholestasis. Hyperthyroidism has previously been reported to be associated with neonatal cholestasis only in single case reports.<sup>6-8</sup>

Neonatal Graves' disease refers to congenital hyperthyroidism in infants from mothers with Graves' disease. It is estimated that 0.2% of pregnant women have Graves' disease, but fetal and neonatal hyperthyroidism occurs in only 1-2% of these children.<sup>9,10</sup> The pathogenesis is believed to be due to transplacental passage of maternal TSHR-Ab, which can also occur in a previously treated mother after thyroid ablation because the TSHR-Ab is produced indefinitely.<sup>7</sup> Maternal TSHR-Ab concentration in the third trimester correlates



**Figure 2.** Trend of FT4 and TSH over time.

to the likelihood of developing neonatal Graves' disease,<sup>11</sup> which is usually transient and resolves spontaneously in 3-12 weeks, as maternal TSHR-Ab clears the infant's bloodstream. The variability in time to clearance is likely dependent on the maternal level of TSHR-Ab in the third trimester.

Typical manifestations of neonatal Graves' disease include low birth weight, preterm birth, microcephaly, frontal bossing, tachycardia, tachypnea, irritability, goiter, hepatosplenomegaly, and exophthalmos. If the diagnosis is confirmed, treatment options include methimazole, beta-blockers, and iodine. Long-term risks of this condition include intellectual impairment, developmental problems, growth retardation, and craniosynostosis.<sup>12</sup> It is unclear what relationship the adequacy of treatment has with development of these sequelae. Our patient demonstrated prematurity, mild exophthalmos, tachypnea, and irritability, but did not have other clinical manifestations of neonatal Graves' disease. At 1 year of age, no delayed development, growth impairment, or craniosynostosis have been observed.

Hyperthyroidism is a rare but reported cause of neonatal cholestasis. In contrast to other reports, which describe cases when mothers were treated with propylthiouracil or radioablation, this is the first reported case of cholestasis in a hyperthyroid neonate of an untreated, undiagnosed mother with Graves' disease. Importantly, many newborn screenings only describe high TSH levels as abnormal. As in this case, low or undetectable TSH levels may be falsely interpreted as normal, which may ultimately lead to a delay in diagnosis. One solution may be to include FT4 routinely in neonatal screening, or as a reflex lab for both high and low TSH.

### Disclosures

Author contributions: RU Varier conceptualized, drafted, and approved the final manuscript, and is the article guarantor. MK Jensen, CJ Adams, and LS Book reviewed, revised, and

approved the final manuscript.

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