Thyroid “Vise” in an Infant With Neonatal Graves’ Disease

abstract

On the rare occasion when neonatal goiter is the cause of airway compromise, it typically presents with a palpable neck mass. In the setting of maternal Graves’ disease (GD), fetal and neonatal goiters are most commonly caused by maternal treatment with antithyroid medication, and the goiter resolves within days of initiation of thyroxine replacement in the neonate. We describe an atypical presentation of a patient with severe neonatal GD born to a euthyroid mother at 35 weeks’ gestational age with respiratory compromise, symptoms of hyperthyroidism, and a nonpalpable thyroid gland. The mother had a history of GD treated with radioactive iodine ablation; during the pregnancy she was treated with levothyroxine throughout and propylthiouracil beginning at 5 months’ gestation, for fetal tachycardia. Laboratory testing after birth confirmed neonatal GD. The patient was treated with methimazole, Lugol’s solution, and levothyroxine, and the patient remained euthyroid from day of life 10. After multiple extubation attempts failed, the patient was found on visualization studies to have a large, predominantly posterior, “vise-like” goiter encasing the larynx and upper trachea. The patient was successfully extubated, and all medications were discontinued on day of life 60. The patient remained euthyroid 1 month after discontinuation of treatment. The patient’s atypical presentation illustrates the need for early neck imaging in patients with neonatal GD and respiratory distress, especially when the thyroid gland is not palpable. Treatment options for resolving a goiter due to neonatal GD are not clear. Pediatrics 2013;132: e1048–e1051

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KEY WORDS
neonatal Graves’ disease, thyroid, goiter, respiratory failure

ABBREVIATIONS
CHF—congestive heart failure
DOL—day of life
GD—Graves’ disease
IVIG—intravenous immunoglobulin
MRI—magnetic resonance imaging
T3—triiodothyronine
T4—thyroxine
TSH—thyroid-stimulating hormone
TSI—thyroid-stimulating immunoglobulin

Dr Regelmann wrote the initial abstract and draft of the case report; Dr Sullivan contributed to the editing and the addition of reference material; Dr Rapaport helped develop the initial outline and significantly contributed to the content and editing of the case report; and all authors approved the final manuscript for submission.

doi:10.1542/peds.2012-3000

Accepted for publication May 31, 2013

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).
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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.
Maternal thyroid disease during pregnancy is not unusual, with rates of hypothyroidism reported to be 2.2% and hyperthyroidism between 0.3% and 0.5%; however, neonatal complications due to maternal thyroid disease are rare. Neonatal hypothyroidism due to transplacental passage of maternal antibodies occurs in 1 in 180,000 live births. Estimates of the frequency of antibodies occurs in 1 in 180,000 live births.2 Neonatal hypothyroidism due to maternal Graves’ disease (GD) vary widely, with estimates of 6 to 24 in 10,000 live births.3 Neonatal goiter has been reported in association with neonatal GD, and airway compromise has been described in hypothyroidism-associated neonatal goiter. Neonatal goiter associated with hypothyroidism causing airway compromise are lacking. We present a patient with a nonpalpable thyroid gland and prolonged, severe airway compromise, due to a predominantly posterior, “vise-like” goiter.

PATIENT PRESENTATION
The patient was a girl born at 35 weeks’ gestational age to a mother with a history of GD treated less than 2 years before the pregnancy with iodine-131 ablation. A previous pregnancy, before the mother’s iodine-131 ablation, produced a child with neonatal GD who needed transient treatment with propylthiouracil shortly after birth. Throughout the patient’s prenatal course, the mother was reportedly euthyroid and treated with levothyroxine. During the fifth month of gestation, the patient was noted to have fetal tachycardia, and the mother was treated with propylthiouracil in addition to the levothyroxine. Subsequent ultrasound studies showed improvement of fetal tachycardia, and because of positioning, the fetal thyroid gland was not visualized during the last month of pregnancy. The remainder of the prenatal course was uneventful. The patient was born with meconium staining of the umbilical cord, had a weak cry and stridor, and shortly after birth needed respiratory support, including endotracheal intubation. Apgar scores were 3, 6, and 7 at 1, 5, and 10 minutes, respectively. Birth weight was 3.14 kg, length 47 cm, and head circumference 33 cm, all appropriate for gestational age. The patient was noted to have tachycardia with congestive heart failure (CHF). The cardiac ejection fraction was 10%, necessitating treatment with dopamine, milrinone, and epinephrine within the first few hours of life. The physical examination revealed a small anterior fontanelle, exophthalmos, and a nonpalpable thyroid gland.

Initial laboratory studies indicated a hyperthyroid state with low thyroid-stimulating hormone (TSH) in the first days of life. The total triiodothyronine (T3) and total thyroxine (T4) and free T4 were elevated. The normal physiologic surge in T4 noted in the first few hours of life may have contributed to the values noted. Thyroid-stimulating immunoglobulin (TSI) and TSH receptor antibodies were strongly positive. Treatment with a β-blocker failed because of poor perfusion, and the patient was transferred to an outside hospital for 2 days because of concerns that extracorporeal membrane oxygenation may have been needed. Ultimately, the patient did not need extracorporeal membrane oxygenation.

Upon transfer back to our institution, on day of life (DOL) 4, cardiac function had improved, and all cardiac medications had been discontinued. At DOL 5, the repeat thyroid function tests were consistent with neonatal GD (Table 1). The patient was started on methimazole 1 mg/kg per day divided every 8 hours, and the next day, a 4-day course of Lugol’s solution 8 mg every 8 hours was instituted. Within 4 days, the thyroid function tests were consistent with a euthyroid state (Table 1), and the CHF had entirely resolved on echocardiogram.

Levothyroxine treatment was started on DOL 27 to maintain euthyroid status. Despite normal thyroid function tests, resolution of CHF, and minimal mechanical ventilation support, between DOL 10 and 17 multiple extubation attempts failed. Magnetic resonance imaging (MRI) of the neck, on DOL 18, revealed a predominantly posterior “vise-like” goiter encasing the larynx and upper trachea (Fig 1). The degree of airway compromise could not be assessed because the patient was intubated at the time of the MRI. The patient was subsequently treated with a 3-day course of dexamethasone 0.25 mg/kg per dose every 8 hours. Serial ultrasounds of the neck over the subsequent 4 weeks showed slow decline in the thyroid lobe volumes, from 5.19 mL to 2.2 mL on the right and 5.59 mL to 2.5 mL on the left. TSI trended down but remained positive at DOL 41 (Table 1).

Extubation attempts continued to fail, and the patient needed mechanical ventilation on minimal settings. On DOL 52, the patient was transferred to an outside hospital for a second opinion about a recommended tracheostomy. At the outside hospital, bronchoscopy revealed tracheal swelling and scar tissue, presumably because of multiple intubation attempts; the scar tissue was removed, and the trachea was treated with topical steroids on 2 occasions. Extubation to room air was successful on DOL 60. The patient remained euthyroid from DOL 10 with a combination of methimazole and levothyroxine until both were discontinued at 2 months of life. At 3 months of life, the patient continued to be euthyroid with no medical intervention.

DISCUSSION
Neonatal goiter can rarely result in airway compromise and is typically associated with a large, palpable neck mass and hypothyroidism. Airway compromise caused by retropharyngeal goiter.
has previously been described in a full-term girl with elevated TSH and respiratory status improved 2 days after initiation of levothyroxine treatment. In hypothyroidism, the lack of negative feedback to the hypothalamus and pituitary caused by low T3 and T4 leads to elevated TSH, which in turn stimulates thyroid growth and development of the goiter. Treatment with levothyroxine decreases the TSH and the stimulation of thyroid growth. When the euthyroid state is achieved, the goiter resolves, and in cases of airway compromise, respiratory symptoms resolve.

The patient had a markedly elevated TSI level at 62 hours of life. This suggests that despite having thyroid ablation and being euthyroid on treatment with levothyroxine during pregnancy, the mother had antibodies that crossed the placenta and led to the neonatal GD. The patient’s TSI levels slowly trended down to normal by DOL 53, but at least through DOL 39, the patient had elevated TSI. The euthyroid state was maintained with a combination of methimazole and levothyroxine until TSI levels normalized. Treatment of neonatal GD can establish the euthyroid state but does not remove the stimulating antibodies, which are thought to be the primary cause of the goiter. Dexamethasone, alone with methimazole and levothyroxine, was associated with a loss in volume of 50% in the thyroid lobes in a 4-week period, although the lobes remained more than 3 times larger than the average volume expected for a full-term neonate. There is no standard treatment, beyond establishment of the euthyroid state, to decrease the size of

<table>
<thead>
<tr>
<th>Age</th>
<th>Free T4 (0.6–1.10 ng/dL)</th>
<th>Total T4 (6.1–12.2 μg/dL)</th>
<th>Total T3 (87–178 ng/dL)</th>
<th>TSH (0.34–5.60 μIU/mL)</th>
<th>TSH Receptor Antibody (&lt;10 U/mL)</th>
<th>TSI (&lt;125%)</th>
<th>Treatment (all oral medications)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 h</td>
<td>16.6</td>
<td>573</td>
<td>0.02</td>
<td>&gt;405</td>
<td>343 (62 h)</td>
<td>Methimazole 1 mg/kg per day ÷ q8h</td>
<td>48</td>
</tr>
<tr>
<td>13 h</td>
<td>1.50</td>
<td>&gt;6</td>
<td>28.8</td>
<td>0.02</td>
<td>190</td>
<td>Methimazole 0.67 mg/kg per day ÷ q12h</td>
<td>48</td>
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<tr>
<td>DOL 5</td>
<td>1.20</td>
<td>145</td>
<td>0.20</td>
<td>48</td>
<td>215</td>
<td>Methimazole 0.5 mg/kg per day ÷ q12h</td>
<td>48</td>
</tr>
<tr>
<td>DOL 10</td>
<td>0.80</td>
<td>163</td>
<td>0.16</td>
<td>48</td>
<td>215</td>
<td>Dexamethason 0.25 mg/kg per dose q8h × 3 d</td>
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<tr>
<td>DOL 22</td>
<td>0.80</td>
<td>145</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>DOL 25</td>
<td>0.80</td>
<td>145</td>
<td></td>
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<tr>
<td>DOL 26</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>DOL 27</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>DOL 32</td>
<td>2.0</td>
<td>5.9</td>
<td>227</td>
<td>0.71</td>
<td>195 (DOL 29)</td>
<td>Methimazole 0.33 mg/kg per day ÷ q12h</td>
<td>48</td>
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<tr>
<td>DOL 36</td>
<td>1.1</td>
<td>10.3</td>
<td>204</td>
<td>0.03</td>
<td>Levothyroxine 4 μg/kg per day</td>
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<tr>
<td>DOL 41</td>
<td>1.0</td>
<td>9.7</td>
<td>209</td>
<td>0.06</td>
<td>Methimazole decreased to 0.15 mg/kg per day ÷ q12h</td>
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<tr>
<td>DOL 52a</td>
<td></td>
<td></td>
<td></td>
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<td>DOL 53</td>
<td>0.11</td>
<td>102 (DOL 53)</td>
<td>Methimazole increased to 0.47 mg/kg per day ÷ q8h</td>
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<td>~DOL 53–55</td>
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<tr>
<td>DOL 59a</td>
<td>1.3</td>
<td>10.7</td>
<td>0.09</td>
<td>Levothyroxine increased to 6.5 μg/kg per day</td>
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<td></td>
<td></td>
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<td>DOL 60</td>
<td>1.0</td>
<td>10.6</td>
<td>145</td>
<td>0.09</td>
<td>Methimazole 0.13 mg/kg per day ÷ q12h</td>
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<td></td>
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<tr>
<td>DOL 93b</td>
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<td>10.6</td>
<td>145</td>
<td>0.09</td>
<td>Methimazole 1.6 μg/kg per day</td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>

Thyroid function tests from 2.5 h to DOL 41 were performed at Mount Sinai Hospital Laboratory, and reference ranges are noted in parentheses. TSH receptor antibody and TSI were measured at Quest Diagnostics, Inc unless otherwise noted.

a Laboratory samples from DOL 52–59 were performed at ARUP Laboratories; reference ranges are as follows: TSH 0.98–5.63 mIU/mL, free T4 1.1–2.2 ng/dL, and total T4 8.1–16.5 μg/dL.

b Laboratory samples from DOL 93 were performed at Quest Diagnostics, Inc; references ranges are as follows: TSH 0.80–8.20 mIU/L, free T4 not established for age, total T4 8.1–15.7 μg/dL, and total T3 not established for age.

**FIGURE 1** MRI of the neck. A, Coronal image. B, Sagittal image. Arrows point to the thyroid tissue surrounding the trachea.
neonatal goiter more rapidly. Because GD-related antibodies can remain in the neonatal circulation for up to 12 weeks,10 the concern was that the thyroid gland was continuing to be stimulated. Given the potential complications of prolonged intubation and mechanical ventilation, several treatment options were considered, including dexamethasone, intravenous immunoglobulin (IVIG), and exchange transfusion. IVIG and exchange transfusion were not used because they were considered to have higher risks. Lewis et al reported using an exchange transfusion to treat neonatal GD complicated by hemolytic disease. Their patient did not have a goiter reported, but the hemolytic disease did improve with the exchange transfusion, suggesting a decrease in circulating antibodies.11 Although IVIG is used to treat GD ophthalmopathy,12 reports of its use in patients with neonatal GD were not found. Our team ultimately decided to treat with a brief course of dexamethasone because it has been established to decrease airway edema for extubation13 and has been used in treatment of GD in older patients, with resulting improvement in goiter.14 Whether the goiter improved more rapidly because of the dexamethasone is unclear.

The early respiratory compromise the patient experienced was probably related to the goiter. Although the patient had tracheal swelling and scar tissue noted after multiple failed extubation attempts, this was presumably not present shortly after birth, when the initial attempts to extubate failed. The patient report demonstrates that an occult goiter should be considered in neonates with unexplained airway obstruction, particularly those with, or at risk for, thyroid function abnormalities.

CONCLUSIONS

The patient had a nonpalpable yet unusually large, predominantly posteriorly located goiter, constricting the trachea and larynx and causing prolonged airway compromise despite rapid achievement of euthyroid status. The presentation illustrates the need for early neck imaging in neonatal GD with respiratory distress, especially when the thyroid gland is not palpable. Future studies to evaluate the best means of treating goiters associated with neonatal GD are needed.

ACKNOWLEDGMENT

We are grateful for the expert clinical care provided by the Mount Sinai Division of Newborn Medicine and especially Dr Kathleen A. Gibbs.

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Pediatrics 2013;132;e1048

DOI: 10.1542/peds.2012-3000 originally published online September 16, 2013;
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