Pediatric Thyroid Disorders:
Is that a lump in your throat?

Christopher Blunden, MD FAAP
Section of Pediatric Endocrinology – Ochsner Health Center for Children
15th Annual Update in Pediatrics CME Conference
July 20, 2019
Disclosures

- None
Objectives

Disorders of Thyroid Gland Development and Hormone Synthesis
- Recognize manifestations of abnormal embryologic development of the thyroid gland
- Identify potential pitfalls in the production of thyroid hormone
- Explain the role of thyroid hormone in maintaining normal metabolism

Congenital Thyroid Disease
- Interpret thyroid function testing results from newborn screening labs
- Recognize the clinical features of congenital hypothyroidism and neonatal Graves’ disease
- Identify the most common etiologies of congenital hypothyroidism
- Understand the natural history and clinical impact of untreated congenital hypothyroidism
- Plan the appropriate diagnostic evaluation and treatment for infants with congenital hypothyroidism and neonatal Graves’ disease.

Autoimmune Thyroid Disease
- Recognize the clinical features associated with autoimmune hypo and hyperthyroidism
- Identify the causes of autoimmune hypo and hyperthyroidism
- Plan the appropriate diagnostic evaluation of autoimmune hypo and hyperthyroidism
- Understand the management options for autoimmune hypo and hyperthyroidism

Non-Autoimmune Thyroid Disease, Thyroid Nodules and Thyroid Cancer
- Recognize other acquired causes of abnormal thyroid function
- Plan the appropriate evaluation of thyroid nodules
- Describe two types of thyroid cancer and the prognosis for each
Disorders of Gland Development and Thyroid Hormone Synthesis
Thyroid Gland Development

- Descends from foramen cecum early in 1st trimester
- Failure of migration leads to lingual thyroid
  - Monitor for obstruction
- Failure of thyroglossal duct to involute leads to thyroglossal duct cyst
  - Diagnosis: Ultrasound
  - Risk of infection and malignancy → Surgical removal recommended

Images from embryology.med.unsw.edu.au and pedclerk.uchicago.edu
Thyroid Hormone Synthesis

TPN $\neq I^-$

$+ \quad = \quad \uparrow \uparrow \quad I^-$

Images from sciencedirect.com and pathologyoutlines.com
Thyroid-CNS Axis

• Production of thyroid hormone is dependent on CNS signals from the hypothalamus (TRH) and pituitary (TSH) and negative feedback.

• TSH deficiency = secondary hypothyroidism = central hypothyroidism or inappropriately normal TSH.

• Resistance to thyroid hormone (RTH).

Table 3: Association between antiepileptic drugs and low fT4.

<table>
<thead>
<tr>
<th>Number of AEDs (n, %)</th>
<th>Low fT4 n=52</th>
<th>Normal fT4 n=246</th>
<th>p value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5(5.2)</td>
<td>92(94.8)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>17(14.5)</td>
<td>98(85.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>30(34.5)</td>
<td>56(65.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AEDs
- PHT (n, %): 18(24.0) vs 57(76.0), 0.084, 1.755, 0.922-3.341
- CBZ (n, %): 29(30.9) vs 65(69.1), <0.001, 3.511, 1.896-6.503
- VPA (n, %): 13(12.0) vs 95(88.0), 0.063, 0.530, 0.269-1.044
- LTG (n, %): 20(19.6) vs 82(80.4), 0.479, 1.250, 0.674-2.320
- TPM (n, %): 15(30.6) vs 34(69.4), 0.008, 2.528, 1.254-5.094
- LEV (n, %): 29(25.7) vs 84(74.3), 0.004, 2.432, 1.325-4.464
- PHB (n, %): 4(18.2) vs 18(81.8), 0.925, 1.056, 0.342-2.359
- OXC (n, %): 4(11.4) vs 31(88.6), 0.318, 0.578, 0.195-1.714

Abbreviations: n, number of cases; OR, odds ratio; CI, confidence interval; SD, standard deviation; PHT, phenytoin; CBZ, carbamazepine; VPA, valproate; LTG, lamotrigine; TPM, topiramate; LEV, levetiracetam; PHB, phenobarbital; OXC, oxcarbazepine; AED, antiepileptic drug; fT4, free thyroxine.

Shih et al. Effects of antiepileptic drugs on thyroid hormone function in epilepsy patients. Seizure. 2017 May;48:7-10
Thyroid Hormone in Circulation and Cellular Targets

- Binds Thyroid Binding Globulin (TBG) and albumin
  - May be low in liver disease (synthesis problem) or kidney disease (protein wasting problem)
  - Inherited TBG deficiency X-linked
- Low total hormone, but normal amount of free hormone
  - No clinical consequence!

- Free hormone binds nuclear receptor in target cells all over the body
Congenital Thyroid Disease
Newborn Screening for Congenital Hypothyroidism

- Stress of birth + cold exposure $\rightarrow$ TSH surge
  - TSH peak within 30-60 minutes after birth, with rise in T3 and T4 in the 1st 24 hrs
- Earlier draw $\rightarrow$ higher likelihood of false positive result
- Prematurity $\rightarrow$ higher likelihood of false negative result
Congenital Hypothyroidism – Prevalence and Etiology

- Approximately 1/2000 infants in the US

- Causes
  - Thyroid dysgenesis (agenesis, ectopy, hypoplasia)
  - Dyshormonogenesis
  - Central hypothyroidism (TSH deficiency)
  - Transient (prematurity, maternal blocking antibodies, maternal iodine deficiency, maternal antithyroid medications)

- Most common cause?? 75-85%
## Congenital Hypothyroidism - Symptoms

### Prevalence of individual symptoms of hypothyroidism at the time of diagnosis.


<table>
<thead>
<tr>
<th>Features listed in questionnaire</th>
<th>Group 2 (n = 232) Initial T4 &gt; 30 nmol/L % with feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged Jaundice</td>
<td>33**</td>
</tr>
<tr>
<td>Feeding Difficulty</td>
<td>16**</td>
</tr>
<tr>
<td>Lethargy</td>
<td>14**</td>
</tr>
<tr>
<td>Umbilical Hernia</td>
<td>18*</td>
</tr>
<tr>
<td>Macroglossia</td>
<td>12*</td>
</tr>
<tr>
<td>Constipation</td>
<td>10</td>
</tr>
<tr>
<td>Cold or mottled skin</td>
<td>10</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>3</td>
</tr>
<tr>
<td>No symptoms</td>
<td>33**</td>
</tr>
<tr>
<td>Other clinical features reported:</td>
<td></td>
</tr>
<tr>
<td>Abnormal cry</td>
<td>6</td>
</tr>
<tr>
<td>Edema</td>
<td>5</td>
</tr>
<tr>
<td>Hypothyroid appearance</td>
<td>6</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>3</td>
</tr>
</tbody>
</table>
Congenital Hypothyroidism - Treatment

- After repeating the lab to confirm an abnormal TSH consider...
  - 1. Immediacy of need
    - Milder TSH elevations with normal T4 may be trended for a short time
    - Significantly elevated TSH and/or low T4 likely indicates permanent disease and greater risk of neurodevelopmental harm with delayed onset of treatment
  - 2. Potential barriers
    - Family reliable? Resource barriers for travel to frequent labs and appointments?
    - Have system in place to ensure no loss to follow-up?
  - 3. Who will counsel family about diagnosis, prognosis, and treatment?
  - 4. Starting dose
    - Levothyroxine 10-15 mcg/kg/day for severe hypothyroidism, 5-10 mcg/kg/day for more mild cases
    - Repeat TSH and T4 in 2 weeks with the goal of normalizing T4 by 2 weeks and TSH by 4 weeks
Levothyroxine

- Brand names - Synthroid, Tirosint, Levoxyl
- T4
  - Converted to T3 by deiodinase enzymes in vivo
- Half-life 4-6 days
  - May double dose next day if missed to maintain steady state
- Pregnancy/OCPs → TBG increase → 50% higher dose needs

Absorption altered by soy, calcium, iron, PPIs
  - If necessary, space out from thyroid hormone
Neonatal Graves’ Disease

- 1-5% of infants born to mothers with Graves’ disease
- Higher antibody titer in 3rd trimester = higher risk
- May have concurrent blocking antibodies causing transient hypothyroidism

Symptoms:
- Low birth weight or prematurity
- Frontal bossing and triangular facies
- Goiter
- Warm skin
- Irritability
- Tachycardia

Resolves spontaneously in 1-2 months once maternal antibodies are cleared

Images from uptodate.com
Autoimmune Thyroid Disease
Case

- A 13 year-old previously healthy female presents for a WCC with the complaint of light periods (menarche at 11) and fatigue. As you review her family history you notice that her paternal aunt has RA. Vitals show a pulse of 60, T 97.4, and BP 92/57. You notice a mildly prominent thyroid with a cobblestone texture on physical exam and decide to draw thyroid function tests.
Case

• A 13 year-old previously healthy female presents for a WCC with the complaint of light periods (menarche at 11) and fatigue. As you review her family history you notice that her paternal aunt has RA. Vitals show a pulse of 60, T 97.4, and BP 92/57. You notice a mildly prominent thyroid with a cobblestone texture on physical exam and decide to draw thyroid function tests.

• TFTs reveal a TSH of 12.2 uIU/mL (0.5-4) and a FT4 of 1.0 (1.0-2.9). Subsequent testing confirms elevated TPO antibody titers.
Hashimoto’s Disease/Chronic Lymphocytic Thyroiditis/Autoimmune Hypothyroidism

- Most common cause of acquired hypothyroidism in the United States
- Increased risk in some genetic and autoimmune conditions:
  - Down syndrome***
  - Turner syndrome
  - Type 1 Diabetes

Other Hypothyroidism Symptoms...

- Poor linear growth
- Goiter
- Dry Skin
- Brittle or thin hair
- Constipation
- Depressed appetite
- Depressed mood
- Fluid retention with **mild weight gain**
- Delayed/precocious puberty***
- Mild End: None
  - “Subclinical hypothyroidism”
- Extreme End: Myxedema coma, pituitary hyperplasia

Symptoms may be preceded by “Hashitoxicosis” - hyperthyroidism from rapid release of colloid stores upon autoimmune attack
Who Wants To Be An Endocrinologist?!?

• What is the syndrome called in which severe primary hypothyroidism induces precocious puberty?
  - Von Wyk-Grumbach syndrome

• What is the pathophysiologic mechanism by which this occurs?
Goiter

• Usually autoimmune-mediated

• Thorough lymph node exam and symptom assessment

• Work-up: TSH, free T4, thyroid autoantibodies

• Ultrasound may not be useful if goiter is uniform

• Symptoms of dysphagia or airway compromise → ENT
• Treatment: Levothyroxine 1.5-2 mcg/kg/day or more with younger age
  – Start lower dose and titrate up in severe cases

• Trend TSH +/- free T4 only for treatment decisions
  – 4-6 weeks after starting treatment and with dose changes
  – If the brain is happy...
Thyroglobulin Ab (TgAb) + in 10.4% of US population >12 years of age – Not associated with clinical thyroid disease

Thyroid peroxidase Ab (TPO) + in 11.3% and is associated with hypo and hyperthyroidism

Hypothyroidism in 4.6% of US population (clinical + subclinical)

FIG. 2. Distribution of TSH results in the second test according to the category of the first TSH measurements in untreated patients (tests were performed between 2002 and 2006).
Hyperthyroidism Illustrative Case

17 yo male presents to adolescent medicine with tremulousness, abdominal pain, dizziness and diaphoresis with standing. Pulse 104, BP 130/84. Labs: TSH 0.051 (L), FT4 of 4.73 (H), + TRAb. Prescribed atenolol, but did not pick up prescription. No-show with Endocrinology. 1 year later presents to ED and found to have fever, n/v, diarrhea, 10# weight loss over 1 week, 10% EF, admitted to PICU on ECMO.
Graves’ Disease Symptoms

- Goiter
- Rapid growth
- Weight loss
- Tremors
- Hyperreflexia
- Palpitations
- Frequent loose stools
- Oily skin and hair
- Lack of concentration
- Ophthalmopathy
- Tongue fasciculations
  - https://www.youtube.com/watch?v=xuwdvBXcr30
- Extreme End: Thyroid storm
  - Fever, delirium, cardiac failure

Images from nejm.org, emedicine.medscape.com
Hyperthyroidism - Biochemical Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3 TOTAL</td>
<td>3.70</td>
</tr>
<tr>
<td>T4</td>
<td>29.7</td>
</tr>
<tr>
<td>T4 FREE</td>
<td></td>
</tr>
<tr>
<td>T4 FREE BY DIRECT ...</td>
<td>&gt;10.0 *</td>
</tr>
<tr>
<td>TSH</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>THYROID STIM IMM</td>
<td>299 *</td>
</tr>
<tr>
<td>TSH REC AB</td>
<td>29.35 *</td>
</tr>
</tbody>
</table>

![Image of thyroid tissue showing normal and Grave's Disease](medcell.med.yale.edu)
Hyperthyroidism - Treatment

• Medical
  – Usually initial treatment
  – Methimazole ONLY
    ☐ Start around 0.5 mg/kg/day divided 1-3 times daily
    ☐ Risk of allergic reaction, agranulocytosis, hepatitis
  – Propothiouricil (PTU)
    → black box warning for hepatotoxicity
  – Beta-blockers
    ☐ Atenolol vs propranolol
  – High dose iodine (Lugol’s)
  – Steroids

• Surgical
  – Ideally by high volume thyroid surgeon (>30/yr)
  – Risks: recurrent laryngeal nerve damage, transient/permanent hypoparathyroidism

• Radioactive Iodine Ablation
  – Goal: Complete gland ablation with conversion to hypothyroid in 4-16 weeks
  – Must be over age 5 and ideally able to swallow a pill
  – Not “block and replace”
Non-autoimmune Acquired Thyroid Disease, Thyroid Nodules, and Thyroid Cancer
Other causes of thyroid disease (or not...)

- Neck/spine/chest radiation
- Status-post BMT
- Iodine load or deficiency
- Adenomas (pituitary or thyroid)
- McCune-Albright Syndrome
- Medications – Lithium, amiodarone
  – Exogenous thyroid hormone intake
  – Heparin
- Obesity – Recommend not checking TSH on routine obesity screening labs without other symptoms or family history of autoimmunity
  – Recommend repeating any TSH <10 uIU/mL with free T4 +/- antibody profile
- Non-thyroidal illness – Do not check TFTs within 1 month of illness

Other causes of thyroid disease (or not...)

Image from emedicine.medscape.com
Thyroid Nodules

History

• Radiation exposure? Family history of thyroid carcinoma? Type?
  Symptoms of thyroid dysfunction?

Exam

• Lymphadenopathy? Goiter?

Labs

• TFTs and antibodies

Imaging

• I-123 Uptake Scan
• Ultrasound TI-RADS →

Biopsy

• Fine needle aspiration biopsy for Bethesda Score →

---

Diagnostic category

I. Nondiagnostic
II. Benign
III. AUS/FLUS
IV. Suspicious for follicular neoplasm
V. Suspicious for malignancy
VI. Malignant
Thyroid Malignancies

- **Follicular and papillary thyroid cancer (DTC)**
  - Excellent prognosis – 98% long term survival, even with recurrent disease
  - Surgery and I-131 as indicated
  - Thyroglobulin levels trended

- **Medullary thyroid cancer**
  - Calcitonin-producing C cell malignancy
  - Associated with MEN2A and MEN2B
    - RET oncogene
    - Thyroid cancer, pheochromocytoma, hyperparathyroidism in relatives?
  - Prophylactic thyroidectomy indicated in known carriers
  - 95% survival at 5 years, declines to 15% by 30 years
Acquired Hypothyroidism in Children: A Guide for Families

What is hypothyroidism?

Hypothyroidism refers to an underactive thyroid gland that does not produce enough of the active thyroid hormones triiodothyronine (T3) and thyroxine (T4). This condition can be present at birth or acquired anytime during childhood or adulthood. Hypothyroidism is very common and occurs in about 1 in 1250 children. In most cases, the condition is permanent and will require treatment for life. This handout focuses on the causes of hypothyroidism in children that arise after birth.

The thyroid gland is a butterfly-shaped organ located in the middle of the neck. It is responsible for producing thyroid hormones T3 and T4. This production is controlled by the pituitary gland in the brain via thyroid-stimulating hormone (TSH). T3 and T4 perform many important actions during childhood, including the maintenance of normal growth and bone development. Thyroid hormone is also important in the regulation of metabolism.

What causes acquired hypothyroidism?

The causes of hypothyroidism can arise from the gland itself or from the pituitary. The thyroid can be damaged by direct antibody attack (autoimmunity), radiation, or surgery. The pituitary gland can be damaged following a severe brain injury or secondary to radiation treatment. Certain medications and substances can interfere with thyroid hormone production. For example, too much or too little iodine in the diet can lead to hypothyroidism. Overall, the most common cause of hypothyroidism in children and teens is direct attack of the thyroid gland from the immune system. This disease is known as autoimmune thyroiditis or Hashimoto disease. Certain children are at greater risk of hypothyroidism, including those with congenital syndromes, especially Down syndrome and Turner syndrome; those with type 1 diabetes; and those who have received radiation for cancer treatment.

What are the signs and symptoms of hypothyroidism?

How is hypothyroidism diagnosed?

Simple blood tests are used to diagnose hypothyroidism. These include the measurement of hormones produced by the thyroid and pituitary glands. Free T4, total T3, and TSH levels are usually measured. These tests are inexpensive and widely available at your regular doctor’s office.

Primary hypothyroidism is diagnosed when the level of stimulating hormone from the pituitary gland (TSH) in the blood is high and the free T4 level produced by the thyroid is low. Secondary hypothyroidism occurs if there is not enough TSH, both levels will be low.

Normal ranges for free T4 and TSH are somewhat different in children than adults, so the diagnosis should be made in consultation with a pediatric endocrinologist.

How is hypothyroidism treated?

Hypothyroidism is treated using a synthetic thyroid hormone called levothyroxine. This is a once-daily pill that is usually given for life (for more information on thyroid hormone, see the Thyroid Hormone Administration: A Guide for Families handout). There are very few side effects, and when they do occur, it is usually the result of significant overtreatment.

Your child’s doctor will prescribe the medication and then perform repeat blood testing. The repeat blood testing will not happen for at least 6 to 8 weeks because it takes time for the body to adjust to its new hormone levels. If the medication is working, blood testing will show normal levels of TSH and free T4. The dose of the medication is adjusted by regular monitoring of thyroid function laboratory tests.

You should contact your child’s doctor if your child experiences difficulty falling asleep, restless sleep, or difficulty concentrating in school. These may be signs that your child’s current thyroid hormone dose may be too high and your child is being overtreated.

There is no cure for hypothyroidism; however, hormone replacement