THYROID DISEASE IN CHILDREN

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Neither I nor any immediate family members have any financial interests that may be construed as a conflict of interest with this presentation.
LEARNING OBJECTIVES

At the end of this lecture, participants will be able to:

1. Recognize and evaluate the following conditions in children:
   - congenital hypothyroidism
   - acquired hypothyroidism
   - hyperthyroidism
   - thyroid nodules

2. Initiate treatment for congenital hypothyroidism

3. Treat acquired hypothyroidism
Thyroid Development

• Thyroid gland develops at 24 days gestation
• Starts development at the base of the tongue (foramen cecum)
• Connected to the tongue via thyroglossal duct
• Arises from an outpouching of the foregut (endoderm)
• Genes Involved:
  – NKX2.1 (TTF-1)
  – TTF-2 (FOXE1)
  – PAX-8
Thyroid Development

- Migrates down to the normal location over the thyroid cartilage by 8-10 weeks
- Thyroglossal duct is the remnant; involutes
Lingual Thyroid

Courtesy of Dr. Dennis Brenner
Ectopic Thyroid
<table>
<thead>
<tr>
<th>Percent</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>31%</td>
<td>prolonged jaundice</td>
</tr>
<tr>
<td>23%</td>
<td>umbilical hernia</td>
</tr>
<tr>
<td>21%</td>
<td>constipation</td>
</tr>
<tr>
<td>21%</td>
<td>macroglossia</td>
</tr>
<tr>
<td>19%</td>
<td>feeding problems</td>
</tr>
<tr>
<td>16%</td>
<td>hypotonia</td>
</tr>
<tr>
<td>16%</td>
<td>hoarse cry</td>
</tr>
<tr>
<td>13%</td>
<td>large posterior fontanelle</td>
</tr>
<tr>
<td>10%</td>
<td>dry skin</td>
</tr>
<tr>
<td>5%</td>
<td>hypothermia</td>
</tr>
<tr>
<td>2%</td>
<td>goiter</td>
</tr>
<tr>
<td>40%</td>
<td>delayed bone age</td>
</tr>
</tbody>
</table>
Hypotonia (decreased muscle tone)
Congenital hypothyroidism occurs in 1:4000 infants.
Congenital hypothyroidism

• Worldwide iodine deficiency is the most common cause of congenital primary hypothyroidism and of preventable mental retardation
Figure 5. Endemic Goiter due to Dietary Iodine Deficiency
Congenital hypothyroidism

- Thyroid dysgenesis - 98% sporadic
- Agenesis: failure of thyroid gland to develop
- Most common in iodine sufficient areas
Pendred syndrome

- Autosomal recessive
- Most common cause of syndromic deafness
- Mutation in chloride-iodide transport protein “Pendrin”
  - Expressed in thyroid & cochlea
- Presents as euthyroid goiter, deafness
Congenital hypothyroidism with goiter due to maternal PTU.
Congenital hypothyroidism

- Maternally transmitted TSH receptor-blocking antibodies (TRB-Ab) can be a cause of transient congenital hypothyroidism
- Incidence approximately 1,100,000
- Transient congenital hypothyroidism resolves in 4-12 weeks
MANAGEMENT OF CONGENITAL HYPOTHYROIDISM

• Documentation
  – Free T4, TSH

• Thyroid scan, ultrasound (optional)

• Treatment (normal size full term)
  – start L-thyroxin at 10-15mcg/Kg daily
  – Monitor TSH every 2-3 months during first 2 years of life.
SYMPTOMS OF ACQUIRED HYPOTHYROIDISM

- Weakness
- Lethargy
- Decreased appetite
- Cold intolerance
- Constipation
- Weight gain
SIGNS OF ACQUIRED HYPOTHYROIDISM

- Goiter
- Growth failure
- Delayed dentition
- Delayed or precocious puberty
- Galactorrhea
- Carotenemia
- Pale dry skin
Girl with TSH of 366.51
All forms of thyroid disease are more common in children with Down syndrome.
EVALUATION OF ACQUIRED HYPOTHYROIDISM

• Documentation
  – TSH
  – Free T4
  – Microsomal antibodies
TREATMENT OF ACQUIRED HYPOTHYROIDISM

- L-thyroxine
  - start with a low dose
  - 0.025 or 0.05 mg daily
- Monitor TSH level every 4 - 6 weeks
- Increase L-thyroxine by 0.0125 mg increments until TSH is normal.
- Monitor TSH every 6 months
Euthyroid Sick Syndrome

- Changes in thyroid function occur within 12 hours of illness
- The lower the T3 the more severe the illness
Euthyroid Sick Syndrome
New insights toward the acute non-thyroidal illness syndrome
Front. Endocrinol., 26 January 2012
SICK EUTHYROID SYNDROME

T4  T3  rT3  TSH

Sick euthyroid  Low  Low  High  Low or Normal

Hypothyroidism  Low  Low  Low  High
CAUSES OF HYPERTHYROIDISM

• Excess production of T4
  – Graves’ disease
  – toxic adenoma
  – pituitary resistance to T4
  – McCune-Albright syndrome
  – TSH receptor mutations
  – TSH producing pituitary tumor

• Excess release of T4
  – Subacute thyroiditis
  – Hashimoto’s toxic thyroiditis
  – iodine induced hyperthyroidism
SIGNS AND SYMPTOMS OF GRAVES’ DISEASE IN ADOLESCENTS

- 98% goiter
- 82% tachycardia
- 82% nervousness
- 80% increased pulse pressure
- 65% proptosis
- 60% increased appetite
- 52% tremor
- 50% weight loss
- 30% heat intolerance
Graves’ disease
EVALUATION OF HYPERTHYROIDISM

- Documentation
  - Free T4, TSH
- Determine etiology
  - thyroid stimulating immunoglobulins
  - radioactive iodide uptake scan
TREATMENT OF GRAVES’ DISEASE

- Antithyroid medications
  - PTU 5-10 mg/Kg divided t.i.d.
    - Not recommended due to liver toxicity
  - Methimazole 0.5-1 mg/Kg daily
- $^{131}$I radioactive ablation
- Thyroidectomy
SIDE EFFECTS OF ANTITHYROID DRUGS

- Rash
- Nausea
- Headache
- Puritis
- Lupus
- Arthritis
- Alopecia
- Hepatic toxicity
- Agranulocytosis
Anti-idiotype antibody

It is possible to make an antibody that is directed against the antigen binding site of another antibody (i.e., the antigen binding site is the epitope). This type of antibody is called an anti-idiotype antibody. In this case, the antigen binding site of the anti-idiotype antibody can be similar in structure to the original antigen (they both recognize the same antibody.)
STIMULATING AUTO-ANTIBODIES (Graves’ disease)

- Pituitary gland
- TSH (Thyroid stimulating hormone)
- TSH receptor
- Auto-antibody to receptor
- Thyroid cell
- Regulated production of thyroid hormones
- Unregulated overproduction of thyroid hormones

Negative feedback control
Neonatal Graves’ Disease
Fetal Thyroid Dynamics

• Early in gestation T4 crosses the placenta from mother to fetus
• Late in gestation fetal T4 is almost exclusively from fetus
• Fetus makes T4 prior to TSH
Thyroid Autoantibodies in Pregnancy

- Up to 20% of pregnant mothers have thyroid autoantibodies
- Risk from thyroid autoantibodies
  - Maternal hypothyroidism
  - Preeclampsia
  - Placental abruption
  - IUGR
Neonatal Thyrotoxicosis

- Life threatening neonatal emergency
- 10% of infants born to mother with Graves disease have increased thyroid hormone
- Neonatal thyrotoxicosis occurs in 1-2% of neonates born to mothers with Graves disease
- Due to transplacental passage of TSI
- Mother can have active or inactive Graves
- All mothers should have TSI levels done at end of 2\textsuperscript{nd} trimester
- TSI greater than 500% strongly correlated
Neonatal Thyrotoxicosis

- Onset is usually day 2-9 of life
- If Thyrotropin Binding Inhibitory Immunoglobulins (TBII) also present can be delayed for 4-6 weeks
SIGNS AND SYMPTOMS OF NEONATAL GRAVES’ DISEASE

- Premature birth
- Low birth weight
- Goiter
- Restlessness and irritability
- Fever, flushing
- Tachycardia, cardiomegally, heart failure
- Lid retraction, proptosis, periorbital edema
- Poor weight gain, or weight loss
- Increased gastrointestinal motility, frequent stooling
Neonatal Graves’ disease
Question- Neonatal Hyperthyroidism

- A baby girl born at term weighing 3500 gm. No prenatal problems or problems with delivery. She is now 14 hours old and has a blood sugar 30 mg/dl and is jittery and irritable. In retrospect you find that mother had Graves disease and underwent total thyroidectomy 8 years ago. You suspect neonatal Graves’ disease and order which of the following?
  - A. Thyroid Ultrasound
  - B. Serum thyroglobulin
  - C. TPO antibodies
  - D. Cord blood TSH, thyroid stimulating immunoglobulin
Question 2-Neonatal Graves

• What would you use to treat this baby?
A. Lugol Solution
B. Methimazole
C. Levothyroxine
D. Glucocorticoids
TREATMENT OF NEONATAL GRAVES’ DISEASE

• Acutely may require beta-blocker, prednisone and Lugol’s solution.
• Methimazole 0.5 – 1mg/Kg daily
  – Goal is to completely suppress the thyroid gland
• Must give L-thyroxin
  – Usually start 25mcg daily
    • Adjust to keep free T4 and TSH in normal range
• Treat for 6 months
  – Maternal antibodies will be cleared by that time
  – Stop Methimazole and L-thyroxin at same time.
SUBACUTE THYROIDITIS

• Physical exam
  – painful swelling of the thyroid
  – signs of hyperthyroidism

• Laboratory evaluation
  – high T4, low TSH, high ESR, absent TSI
  – decreased radioactive iodide uptake scan

• Treatment
  – beta blockers
  – ASA, glucocorticoids
Exogenous Thyroid Hormone

- High free T4, high T4, high T3, low TSH
- Can you test for this?
Exogenous Thyroid Hormone

- plasma thyroglobulin level will be undetectable or extremely low in patients chronically abusing thyroid hormone
- may be used to differentiate cause
Autonomous Thyroid Nodule

• Functions independent of normal pituitary control

• Occur from somatic mutations in either the alpha subunit of the G-protein or TSH receptor

• Mutation results in constitutive activation of adenylyl cyclase and unregulated production of cAMP

• Rare in children
Autonomous Thyroid Nodules

- Radionuclide image using I-123 can help differentiate between a hot or cold nodule.
- Hot nodule will accumulate radioisotope in the nodule and decreased or absent uptake in the surrounding tissue.
McCune-Albright Syndrome

- Single or multiple hyperfunctioning adenomatous nodules
- Usually between 3-12 years
- Equal in boys and girls
- Overproduction of LH, FSH, TSH, GHRH, ACTH, and PTH seen in MAS are all receptors that are couple to G-proteins
McCune-Albright Syndrome
McCune-Albright Syndrome
Thyroid nodule
Thyroid Nodules

- 1% of Children
- 26% of thyroid nodules in children are malignant
- US & FNA best tools to identify cancer
- most benign nodules remain benign
- Prevalence of nodules is greater following radiation exposure
- Majority of thyroid cancers in children are papillary thyroid cancer
## Thyroid Nodules in Children

<table>
<thead>
<tr>
<th>Carcinoma</th>
<th>Adenoma</th>
<th>Reference</th>
<th>Year</th>
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<tbody>
<tr>
<td>35%</td>
<td>52%</td>
<td>Hayles</td>
<td>1956</td>
</tr>
<tr>
<td>20%</td>
<td>25%</td>
<td>Adams</td>
<td>1968</td>
</tr>
<tr>
<td>40%</td>
<td>24%</td>
<td>Kirkland</td>
<td>1973</td>
</tr>
<tr>
<td>17%</td>
<td>58%</td>
<td>Scott</td>
<td>1976</td>
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</table>
Question - Thyroid Nodules

15 year old female with 2.8 cm palpable firm mass in the right lobe of the thyroid gland. There is no fever, erythema or tenderness. The free T4 and TSH are normal. Microsomal antibodies are positive. What tests would you order?

a) Thyroglobulin antibody
b) Thyroid ultrasound
c) Serum calcitonin
d) 131 iodine uptake and scan
M.E.N. SYNDROMES

• M.E.N. 1
  – parathyroid, pituitary, and pancreatic adenomas
• M.E.N. 2a
  – medullary thyroid carcinoma, pheochromocytoma, parathyroid adenoma
• M.E.N. 2b
  – medullary thyroid carcinoma, pheochromocytoma, mucosal neuromas, intestinal neuromal dysplasia, marfanoid habitus
• Familial medullary thyroid carcinoma
M.E.N. 2

- **M.E.N. 2a**
  - Due to mutations in the extra-cellular region of the RET receptor.
  - Usually autosomal dominate inheritance.
  - Recommend thyroidectomy at age 3 years.

- **M.E.N. 2b**
  - Due to mutations in the intra-cellular region of the RET receptor.
  - Usually sporadic mutations.
  - Earlier development of medullary thyroid cancimoma.
  - Thyroidectomy done as soon as diagnosis made.
MEN 2b
<table>
<thead>
<tr>
<th>Condition</th>
<th>Free T4</th>
<th>TSH</th>
<th>Antibodies</th>
</tr>
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<tbody>
<tr>
<td>Congenital hypothyroidism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>athyrotic</td>
<td>low</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>nonathyrotic</td>
<td>normal / low</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>Acquired hypothyroidism</td>
<td>normal / low</td>
<td>high</td>
<td>microsomal</td>
</tr>
<tr>
<td>Euthyroid sick syndrome</td>
<td>low</td>
<td>normal/ low</td>
<td>absent</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>high</td>
<td>low</td>
<td>T.S.I.</td>
</tr>
<tr>
<td>Subacute thyroiditis</td>
<td>high</td>
<td>low</td>
<td>absent</td>
</tr>
</tbody>
</table>
Question 1
A 16 y.o. girl complains of weight loss, nervousness and tenderness in her anterior neck. Which of the following will clearly differentiate Graves’ disease from subacute thyroiditis?

A  Free T4  
B  T3  
C  TSH  
D  radioactive iodide uptake scan
Question 2
Which of the following medications is NOT helpful in treating subacute thyroiditis?

A  PTU
B  Propanolol
C  Aspirin
D  Prednisone
Question 3
A goiter (thyroid enlargement) is usually **NOT** present in which of the following?

A  Hashimoto’s thyroiditis  
B  Congenital hypothyroidism  
C  Graves’ disease  
D  Subacute thyroiditis
A 15 y.o. girl complains of constipation, tiredness and galactorrhea. On exam you note an enlarged firm thyroid gland. What is the most cost effective blood test to confirm your suspicion of hypothyroidism?

A  TSH
B  T4, TSH, microsomal antibodies
C  Free T4, TSH, prolactin
D  T4, T4RU, TSH, thyroglobulin antibodies
Question 5
A child’s father has M.E.N. 2. Which screening test should be performed?

A  Fasting calcitonin level
B  Calcitonin level after calcium infusion
C  24 hour urine for metanephrines
D  Genetic testing on both the father and child
Question 6
This boy has:
A) just broken a neighbor’s window with his baseball
B) just watched the movie “Halloween”
C) subacute thyroiditis
D) Graves’ eye disease
Graves Ophthalmopathy

- clinically evident in over half of children and adolescents
- Usually mild
- may include
  - lid lag
  - lid retraction
  - stare, proptosis
  - conjunctival injection,
  - periorbital edema
Graves Ophthalmopathy

- explained by mechanical effects of an increase in tissue volume within the bony orbit
- caused by accumulation of glycosaminoglycans (GAGs) in the connective tissue of the orbital fat and muscles
- Orbital fibroblasts are the primary targets of the autoimmune attack and thought to share similar antigen structure with thyroid
Graves Ophthalmopathy

- treatment not needed for mild cases
- eye drops or ointment needed to prevent corneal drying
- severe ophthalmopathy
  - Oral corticosteroids
  - orbital irradiation
  - surgical decompression
Question 7.
An adolescent female complains about her tall stature. On physical exam you notice some nodules on her lips and tongue. She has a history of severe constipation. No other family members have similar problems or findings.

What is your next step.
A. Obtain RET mutation analysis
B. Exam patient’s parents.
C. Obtain calcitonin and CEA levels
D. Obtain Ca++ and PTH levels.
Iz a thyroid problem..
now give me cupcake