58TH Pediatric Postgraduate Course

March 24 -26, 2023 | Loews Hotel, Coral Gables, Florida

Breakout - B206B

Cases I Learned From - 3 Specialties: Dermatology, Endocrinology, Rheumatology

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Nicklaus Children's Hospital

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Disclosure Statement

Drs. Diaz & Sterba have not had (in the past 24 months) any conflicts of interest to resolve or relevant financial relationship with the manufacturers of products or services that will be discussed in this activity or in this presentation.

Dr. Duarte has disclosed relevant financial relationship with the following ineligible companies in the past 24 months.

Professional Services / Pfizer / Speaker
Professional Services / Pierre Fabre / Speaker
Professional Services / Regeneron-Sanofi / Speaker

The speakers do not intend to discuss an unapproved/investigative use of a commercialproduct/device in this presentation.

The speakers will support this presentation and clinical recommendations with the "best available evidence" from medical literature.

Nicklaus Children's Hospital

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Cases I Learned from: Thyroid

PPGC 2023

Chief, Division Pediatric Endocrinology
Associated Professor, FIU

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Disclosures

- I have no relevant financial relationships
- I have no conflicts of interest

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Cases to be Discussed

- Congenital Hypothyroidism
- Hyperthyroidism

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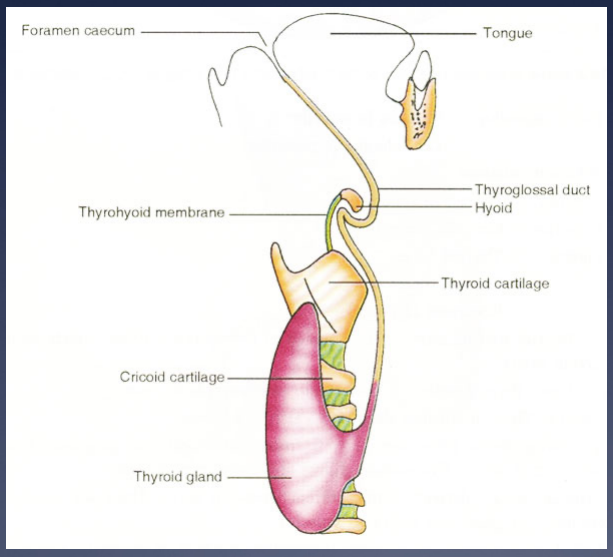
Development of the Thyroid Gland



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Case #1

- 1-week old boy
- Full term, NSVD, BW: 7 lb 5 oz
- Newborn screening:
  - TSH 45 mIU/L, T4 14 ng/dL
- Unremarkable pregnancy and family history. Mother without h/o thyroid problems
- Normal physical examination

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Congenital Hypothyroidism (CH)

- Incidence: 1:2,000-4,000 newborns
  - Higher prevalence in Asians, Native American, and Hispanics
  - Higher incidence in females and infants with trisomy 21
- Majority of newborns with CH do not have obvious manifestations of hypothyroidism
- Neurodevelopmental outcome is inversely related to the age of diagnosis and treatment

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Etiology of Congenital Hypothyroidism

- Primary Congenital Hypothyroidism
  - Thyroid dysgenesis: ectopia, aplasia, hypoplasia
  - Thyroid dyshormogenesis (AR, goiter)
    - Na-iodide symporter, TPO, Thyroglobulin, deiodinase defects
  - Iatrogenic: RAI after week 10th of gestation

Diaz, Peds in Review 2014

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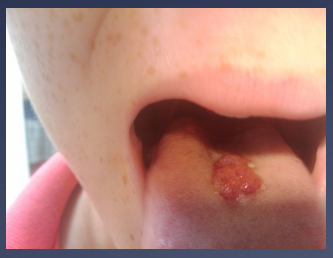
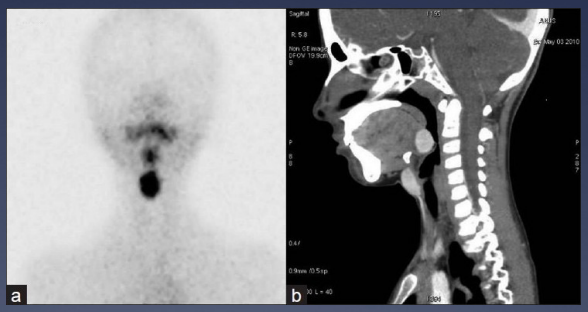
Ectopic Thyroid Gland





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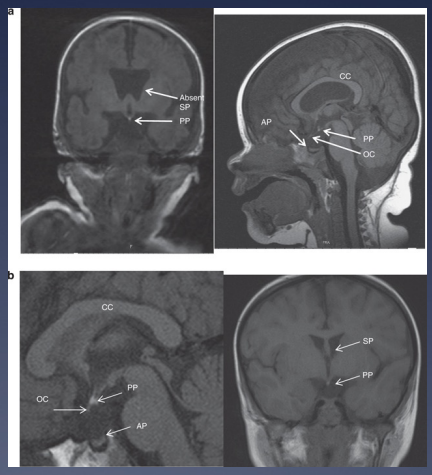
Central Hypothyroidism

- TSH may be low, normal or slightly elevated with low T4/free T4
- 1:16,000-1:25,000
- Blindness/nystagmus (SOD), hypoglycemia, hyperbilirubinemia, microphallus, and/or cryptorchidism



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Evaluation of Congenital Hypothyroidism (NBS)

- Dried blood spot: 48 to 72 hours of age (TSH surge 60-80 mIU/L)
- Take always before blood transfusion
- Florida NBS: TSH and T4 (recall rate 0.3%)
- Infants born preterm or LBW have lower T4 and reduce TSH surge
- Delayed TSH rise (1:54-95 w<1,500 g; 1:737 w: 1,500-2,500 g
- Nonthyroidal illness: acute illness, preterm or LBW: low T4 with normal TSH (same as TBG deficiency)

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Congenital Hypothyroidism

- Confirmatory test in any child whose NBS suggest CH
  - Physical examination: goiter, lingual thyroid, etc.
  - Check TSH and FT4
  - Elevated TSH and normal FT4 (subclinical hypothyroidism)
    - If TSH>20 mIU/L: start Tx
    - If TSH: 10-20 mIU/L: start Tx or repeat every 1-2 weeks
    - If TSH: persists >10 mIU/L: start Tx
    - If TSH: 5-10 mIU/L >4 weeks: insufficient evidence to support Tx

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Congenital Hypothyroidism

- Confirmatory test in any child whose NBS suggest CH
  - Normal TSH and low T4
    - Central hypothyroidism (it is not mild hypothyroidism)
    - Non-thyroid illness
    - Prematurity
    - LBW
    - TBG deficiency: check FT4 and/or TBG level

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Congenital Hypothyroidism

- Imaging
  - Thyroid US: presence or location of thyroid gland without exposure to radiation
    - Elevated TSH, eutopic gland with low **thyroglobulin:** thyroglobulin synthesis defect or TSH receptor signaling (maternal TRBAb, mutation of TSHR, or GNAS)
    - Enlarged, eutopic gland, with low thyroglobulin: dyshormogenesis

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Congenital Hypothyroidism

- Imaging
  - Scintigraphy: better at detecting ectopic thyroid tissue
    - If TSH less than 30 mIU/L or >20 days of Tx (low uptake)
    - Absence of eutopic gland:
      - Thyroid aplasia/hypoplasia
      - Exposure to excess iodine
      - Genetic iodine transport defect
      - Defect in TSHR signaling (including maternal TRBAvb, mutations TSHR or GNAS)
    - Iodine uptake and enlarged gland
      - Dyshormogenesis
  - If normal imaging: may have transient hypothyroidism

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Congenital Hypothyroidism

- Genetic testing
  - Thyroid dysgenesis
    - usually sporadic
    - Rarely caused by genetic mutations (frequently associated with other abnormalities)
  - Thyroid dyshormogenesis
    - Usually caused by genetic mutations: TSHR signal transduction, iodide transport or organification
  - Central hypothyroidism
    - Mutations in transcription factors: HH development 75% (multiple pituitary deficits): *HESX1, LHX3, LHX4, SOX3, OTX2, PROP1, POU1F1*
    - Isolated central hypothyroidism: rare
      - *IGSF1* (macroorchidism), *TSHB, TBL1X, IRS4*

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Congenital Hypothyroidism

Associated congenital anomalies in 10%

- Hearing loss: 10% of children with CH
- Cardiovascular
  - Pulmonary stenosis
  - ASD and VSD
- Neural tube defects
- Hip dysplasia
- Renal/urinary tract anomalies

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Treatment of Congenital Hypothyroidism

- Levothyroxine 10-15 mcg/kg/day PO
- If IV LT4 needed: use 75% of the PO dose
- Check TSH 2 weeks later
- Goal to have a TSH <5 mIU/L
- Persistent elevated TSH (central resistance to TH due to intrauterine hypothyroidism)
- Normalize TSH vs FT4?
- Adding LT3 may normalize TSH and FT4

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Monitoring Treatment of CH

- Check TSH and FT4 every:
  - 1-2 months: 1st 6 months of life
  - 2-3 months: 2nd 6 months of life
  - 3-4 months between 1-3 years of life
- If eutopic thyroid gland: d/c LT4 at 3 years and check TSH/FT4 1 month later
  - 40% have permanent hypothyroidism
  - 25% have subclinical hypothyroidism
  - 35% recovered (transient hypothyroidism)

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Causes of Transient CH

- Maternal Graves disease
  - MMI, PTU, carbimzole cross the placenta (7-10 days)
  - TRBab (2% of CH) (3-6 months)
  - Untreated maternal hyperthyrodism
- Iodine deficiency
- Iodine excess
  - Wolff-Chaikoff effect
  - Maternal use of amiodarone
  - Iodine-containing antiseptics
  - Radiologic contrast agents
  - Excessive maternal iodine intake

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An infant with cretinism. Note the hypotonic posture, coarse facial features, and umbilical hernia.

Close-up of the face of the same infant. Note the macroglossia.

The infant a few months after starting thyroid hormone replacement.

Close-up of the same infant few months after starting thyroid hormone replacement.

Images from emedicine.medscape.com/article/919758-media

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Our Case

- 1-week old boy
- Full term, NSVD, BW: 7 lb 5 oz
- Newborn screening (sample taken at 20 hours of life):
  - TSH 45 mIU/L, T4 14 ng/dL
- Repeated labs at 1 week of life:
  - TSH 4 mIU/L, FT4 1.5 ng/dL

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Second Case

- 10-year-old boy with autism
  - New therapies include risperidone and family added biotin 10 mg daily
  - Follow up by psychiatric found a TSH of 0.02 mIU/L and T4 of 15 ng/dl
- Unremarkable history
- PE: BP: 110/60, HR: 80 x min, no ophthalmopathy, no goiter
  - Repeat laboratory testing: TSH 0.01 mIU/L, FT4 3.4 ng/dl (0.9-1.5), TSHRab (positive)

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Hyperthyroidism

Table 2. Potential Diagnoses in Patients with Hyperthyroidism and Suppressed Serum Thyrotropin.*

Condition	Symptoms and Associated Features	Test Results		
		Thyroid-Function Tests	24-hr Radioiodine Uptake and Pattern	Additional Studies and Factors in Evaluation
Graves' disease	Usually symptoms for at least 2–3 mo; thyroid enlargement, thyroid bruit, Graves' ophthalmopathy	Elevated serum T_4 and T_3 (usually higher elevation of T_3 than T_4)	Elevated uptake with homogeneous symmetric distribution	Elevated TSI or thyrotropin-receptor antibodies
Painless thyroiditis	Usually modest symptoms of short duration (<3 mo); can occur in the postpartum period	Elevated serum T_4 and T_3 (usually equal elevation of T_4 and T_3)	Low uptake	Serum thyroid peroxidase antibodies usually positive
Painful subacute thyroiditis	Thyroid tenderness, modest symptoms of short duration; often occurs after a viral illness	Elevated serum T_4 and T_3 (usually equal elevation of T_4 and T_3)	Low uptake	Thyroid-related antibodies usually negative
Toxic multinodular goiter	Variable onset and range of severity; in iodine-sufficient locations, multinodular goiter more common in older persons (approximately >50 yr); in iodine-insufficient locations, may be common in younger persons	Elevated serum T_3; serum T_4 can be low, normal, or high	Increased uptake with patchy distribution	Thyroid-related antibodies usually negative
Solitary hyperfunctioning nodule	Variable onset and range of severity; incidence increases with increasing age; more common in women than in men; usually clinically significant hyperthyroidism when nodule >3 cm in diameter	Elevated serum T_3; serum T_4 can be low, normal, or high	Increased uptake with focal uptake in nodule and suppression in surrounding gland	Thyroid-related antibodies usually negative
Iodine-induced hyperthyroidism	Usually rapid onset of symptoms (hours to days) after exposure to excess iodine (e.g., from a contrast study or medications such as amiodarone)	Elevated serum T_3; serum T_4 can be low, normal, or high	Variable, depending on dose and form of iodine (and time required for excretion) and any underlying thyroid disease	Usually in the setting of an underlying multinodular goiter or in geographic areas of iodine deficiency
Exogenous ingestion of thyroid hormone	Variable, related to duration of ingestion	Reflects content of preparation of thyroid hormone; usually T_4 primarily elevated, although in some preparations both T_4 and T_3 or T_3 alone is elevated	Low uptake	Serum thyroglobulin concentration usually low

N Engl J Med 2008;358:2594-605.

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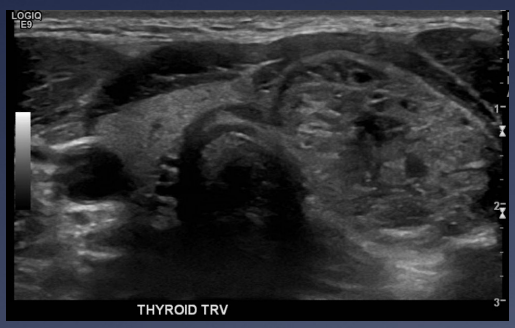
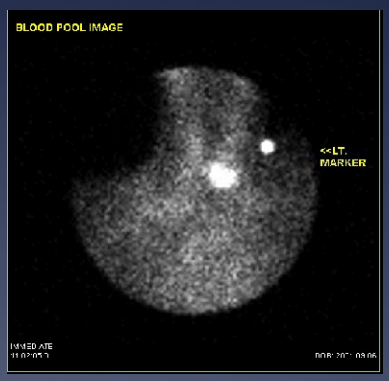
12 y/o Girl with a Thyroid Mass and Suppressed TSH





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Graves Disease

- Graves disease accounts for 10-15% of thyroid disorders in patients < 18 y
- Incidence 0.1-3 per 100,000 children
- Prevalence 1 in 10,000 children in USA
- Peak incidence at 10-15 y
- Diffuse infiltration of lymphocytes into the thyroid gland
- Antibody against the TSH-receptor (TRAb), but often TPO and ATG abs are present (hyper-hypo)

JCEM, March 2011

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TABLE 1. Signs and symptoms of GD in children

Signs	Symptoms
Goiter	Hyperactivity
Tachycardia	Palpitations
Weight loss	Sleep disturbance
Heat intolerance	Fatigue
Tremor	Poor school performance
Systolic hypertension	Emotional lability
Increased pulse pressure	Neck fullness or lump
Hair loss	Irritability and nervousness
Secondary enuresis (nocturia)	Increased stool frequency
Advanced bone age	Increased appetite
Ophthalmopathy—pain, exposure keratitis, lid lag, proptosis	

JCEM, March 2011

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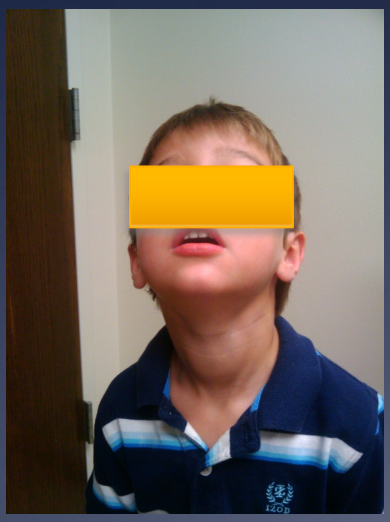
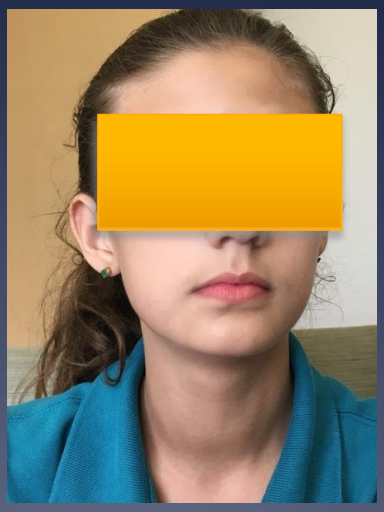
Children with Graves Disease





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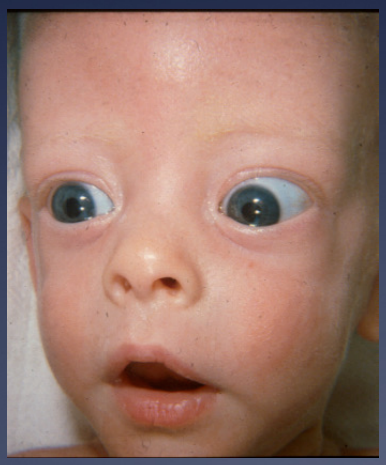
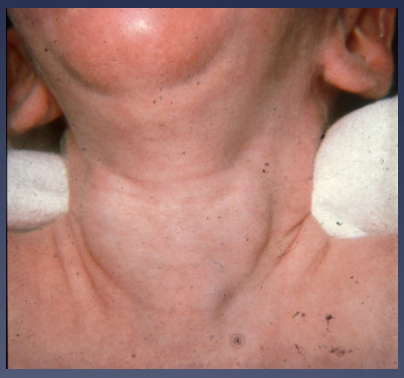
Congenital Graves Disease





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Treatment of Hyperthyroidism

- Medical treatment:
  - Methimazole (MMI) 0.2-0.4 mg/kg/day
  - Beta-blocker:
    - Propranolol 1-2 mg/kg/day
    - Atenolol 0.5-1.2 mg/kg/day
  - Approaches of medical treatment:
    - Titrate
    - Block-and-replace
  - Likelihood of remission ~ 30% (25-65%)

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Treatment Options for Grave Disease

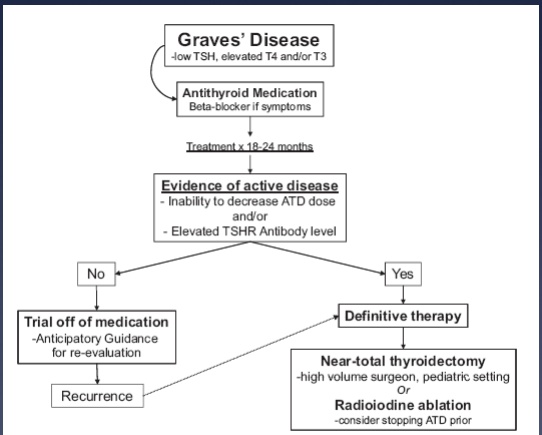

FIG. 1. Treatment options for GD. ATD, Anti-thyroid drug.

JCEM, March 2011

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Our Case

- Discontinuation of biotin
- Repeated labs:
  - TSH 2.5 mIU/L, FT4 1.2 ng/dL (0.9-1.5)
- Biotin (Vitamin B7): daily requirement 30 ug/d
- Currently use of hair loss, nail/skin conditions, MS
- Spurious results in streptavidin/biotin-based immunoassays (thyroid, steroids, hormones, tumor markers, and vitamins)

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Thank You

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