d. Thyroid hormone resistance

1. Pathophysiology

   a. Be aware that mutations in the thyroid hormone receptor beta are associated with thyroid hormone resistance

Thyroid hormone receptors (TR) mediate the action of thyroid hormone within the nucleus. TRs are transcription factors that activate or repress transcription of specific target genes. Mutant TR proteins have reduced ability to bind ligand, protein cofactors, or DNA. Mutation of thyroid hormone receptor beta (TRβ) is the most frequent cause of resistance to thyroid hormone. Interferes with the ability of the thyroid hormone receptor β to properly respond to T3. Inherited in autosomal dominant manner in all but 1 family. Almost all patients have mutations in 1 allele of the TR-beta (TRβ) gene.

   b. Be aware that the presence of different thyroid hormone receptor types in different tissues produce variable effects of this condition upon different tissues of the body

In patients with mutations in the TRβ, all tissues that express TRβ have reduced sensitivity to action of T3. The severity of hormone resistance varies among different tissues in an affected individual, likely due to differences in relative expression of TRβ and TRα in different tissues. In general, patients may have mixed symptoms of hyper- and hypothyroidism. Before the genetic cause was known, TRH was subdivided in to 2 main types:

1) Generalized thyroid hormone resistance:
   - Majority of cases
   - Poor response to thyroid hormone in most or all tissues
   - May have features of hypothyroidism

2) Pituitary resistance to thyroid hormone:
   - Resistance more severe in the hypothalamic-pituitary axis than in the remainder of tissue
   - Causes features of hyperthyroidism

Both groups of clinical symptoms/signs can be seen in individuals with identical TRβ mutations. There are no distinctive laboratory differences between the groups. Organs expressing predominantly TRα include: Bones, Gastrointestinal tract, Heart, Striated muscle, CNS. Tachycardia is more common in TRβ mutations than reduced heart rate, attributed to the fact that thyroid hormone effects in the heart are primarily dependent on the TRα.

2. Clinical implications

   a. Clinical findings

1. Be aware of the clinical findings in thyroid hormone resistance, including attention deficit hyperactivity disorder

Severity ranges from clinically asymptomatic to variable stigmata compatible with thyrotoxicosis and hypothyroidism. Goiter is the most common clinical finding.
Neuropsychologic abnormalities are common in patients with THR:
- 50% of patients having ADHD
- Can have learning disabilities and developmental delay
- Hyperactivity tends to improve with age
Deafness can occur and is thought to be due to necessity of thyroid hormone for normal development of auditory function.
Growth retardation and delayed skeletal maturation can be seen with both mutations.
Most individuals achieve normal stature and development and lead a normal life despite high TH levels and thyroid gland enlargement.

b. Diagnosis
   1. Be aware of the diagnostic approach to thyroid hormone resistance

Definitive diagnosis requires sequencing of the TRβ gene.
Laboratory findings
   - Thyroid hormone receptor beta mutations
     Unusual combination of elevated free T4 and normal or slightly elevated TSH
     Usually accompanied by high T3 and rT3
   - Thyroid hormone receptor alpha mutations
     Low TT4 and rT3, borderline high TT3, and normal or slightly elevated TSH
Differential dx includes RTH and TSH secreting pituitary adenoma
Family history (RTH) and elevated glycoprotein alpha-subunit (TSH secreting adenoma) are helpful in differentiating the 2 diagnoses

c. Treatment
   1. Be aware of the treatments for thyroid hormone resistance

Can be difficult
Treatment with thyroid hormone analogues may worsen the cardiac symptoms.
Beta-blockers can be used to control tachycardia and may improve ADHD
Patients may require additional therapies for ADHD
3,5,3'-triiodothyroacetic acid (TRIAC), a TH analog that suppresses TSH secretion → resulting in decreased thyroid hormone production, has been used in some patients.
   Binds to TRβ, both wild type and mutated, with higher affinity and more efficient activation of transcriptional activity than T3, overcoming the dominant negative effect of mutant receptors.
   Rapidly degraded
   Has similar affinity as T3 for TRα, so that it does not over activate it, bringing the balance of TRα/TRβ function closer to normal
Treatment should be specific to patient’s symptoms, using beta-blockers, thyroid hormone analogues and antithyroid medications as necessary.

2. Thyroid hormone excess

a. Neonatal Graves disease
   1. Pathophysiology
      a. Understand the mechanism of neonatal Graves disease in relation to maternal thyroid disease


A truly overactive thyroid gland is uncommon in established pregnancy, affecting approximately 0.2% of women. The low rate is due to suppression of autoimmune responses during pregnancy, as well as negative influences of hyperthyroidism on fertility and pregnancy loss.

Neonatal hyperthyroidism affects 1-2% of babies born to mothers with GD, which is an incidence approximately four times higher than transient neonatal hypothyroidism due to maternal TSH receptor blocking antibodies.

Mothers often have mixtures of stimulating and blocking antibodies, the relative proportion of which may change over time. The clinical picture in the neonate depends on the relative proportion of stimulating and blocking antibodies transmitted across the placenta and the rate of their clearance from the neonatal circulation postpartum.

Passage of antibodies becomes clinically significant at the end of the second trimester.

Maternal level of TSI is clinically significant, with TSI greater than 35% associated with the development of fetal thyrotoxicosis.

Pregnant women at risk for failure to suppress TSI include those with more severe hyperthyroidism, significant orbitopathy or infiltrative dermopathy.

Antibodies may continue to be produced after ablation of the thyroid by surgery, radioiodine, or by the immune mechanisms of Hashimoto's thyroiditis.

2. Clinical implications
   a. Know the clinical presentation of neonatal Graves disease

   Signs/Symptoms:
   - IUGR
   - Craniosynostosis
   - Irritability
   - Diarrhea
   - Vomiting
   - Tachycardia
   - Arrhythmias
   - Hepatosplenomegaly
   - Hyperviscosity syndrome
   - Compressive sx's due to thyromegaly
   - Nonimmune fetal hydrops
   - Intrauterine death
   - Flushing
   - Poor weight gain
   - Ophthalmopathy
   - Cardiac failure
   - Systemic and pulmonary HTN
   - Jaundice
   - Thrombocytopenia

   b. Know the course of neonatal Graves disease

   Usually presents shortly after birth. Onset may be delayed for 5-10 days in infants whose mothers received antithyroid treatment. There are rare reports of presentations delayed up to 4-6 weeks, likely related to clearance of higher affinity blocking antibodies.

   Spontaneous recovery usually begins within 3 months and is usually complete by 6 months, with clearance of antibodies from neonatal circulation. No reports of recurrence.

   A subset of patients appear to have endogenous production of TSI and remain hyperthyroid for prolonged period of time, often ultimately requiring ablative therapy. Recurrences have
been reported in these patients. Typically come from families with strong history of GD. If persistent hyperthyroidism occurs in the absence of detectable TSI in the maternal and neonatal circulation, suspect gain of function mutation in TSH receptor.

Most cases result from a mutation in exon 10. Many are autosomal dominant, also reports of sporadic development.

c. Be aware of the management of neonatal Graves disease

Asymptomatic
Measurement of the TSI is very helpful and recommended to be done at birth using cord blood. Repeat testing at 5-7 days of life if TSI is positive. May be repeated again at 4-6 weeks.

Symptomatic:
Supportive care including airway maintenance, temp control, fluid balance.
Methimazole 0.5-1 mg/kg/day (PTU 5-10 mg/kg/day) orally divided q8h. Increase dose by 50-100% if no clinical response in 24-48 hrs.
In severe hyperthyroidism iodides may be used as adjuvants to prevent further release of thyroid hormone (Lugol’s solution or SSKI, 1 drop q8h).
Propranolol (2 mg/kg/day in 2 or 3 divided doses) is added if sympathetic overstimulation is severe, particularly in the presence of pronounced tachycardia. If cardiac failure develops, treatment with digoxin should be initiated, and propranolol should be decreased or discontinued.
In severe cases prednisone (2 mg/kg/day) may be added for immediate inhibition of thyroid hormone secretion and decreased peripheral conversion.
ATDs appear in breastmilk but in low concentrations. Both MMI and PTU are approved for nursing mothers by the American Academy of Pediatrics.

b. Childhood Graves disease
1. Pathophysiology
   a. Know about the autoimmune mechanisms involved in the pathogenesis of Graves disease including the various types of TSH receptor antibodies

Autoimmune thyroid disease is characterized by the occurrence in the serum of antibodies against thyroid peroxidase (TPO), thyroglobulin (Tg), and the TSH receptor (TSHR).

The circulating autoantibodies specific to hyperthyroid GD are IgG immunoglobulins, subclass G1. They bind to the extracellular domain of the TSHR and activate signal transduction.

   TRAb (TSH receptor antibody) – does not discriminate between activating and blocking antibodies.
   TSI – specific for TSH activating activity, but not very sensitive.
   TBII - Thyrotropin Binding Inhibitory Immunoglobulins

The thyroid gland itself is the major site of thyroid autoantibody secretion via the B cells that form part of the intrathyroidal infiltrate, however lymphocytes in the spleen, lymph nodes, bone marrow and peripheral blood may also produce antibodies.

   b. Recognize the relationship of Graves disease to other autoimmune diseases of the thyroid with and without hyperthyroidism
Can have both thyroid stimulation autoantibodies (typical of GD) and TPO and TG autoantibodies typical of Hashimotos in the same patient. Unclear what causes GD vs Hashimotos in these patients.

2. Clinical implications
   a. Clinical manifestations

   Symptoms often develop insidiously. Almost all patients have some degree of thyromegaly, which is usually symmetrically enlarged, smooth and nontender. A thyroid bruit may be audible.

   Most have symptoms of excessive thyroid activity: tremors, inability to fall asleep, weight loss despite an increased appetite, proximal muscle weakness, heat intolerance, hands are often warm and moist. Tachycardia, wide pulse pressure, and a hyperactive precordium are common. Shortened attention span and emotional lability may lead to behavioral and school difficulties.

   Increased glomerular filtration rate may lead to polyuria, polydipsia and nocturia.

   Acceleration in linear growth may occur, often accompanied by advancement in bone age. Puberty may be delayed. If menarche has occurred, secondary amenorrhea is common.

   Ophthalmopathy is seen in over half of patients. Symptoms are usually relatively mild and include lid lag, lid retraction, stare, proptosis, conjunctival injection, chemosis, periorbital and eyelid edema. Severe ophthalmopathy is rare and can include severe proptosis, periorbital ecchymosis, corneal ulceration, eye muscle paralysis and optic atrophy.

b. Diagnosis
   1. Differentiate between Graves disease and other conditions involving hyperthyroidism

   The diffuse goiter of Graves’ disease is rarely confused with that of other thyroid diseases if thyrotoxicosis is present.

   Graves disease
   - Low serum TSH concentration and elevated free T4
   - Presence of TSI indicate underlying Graves' disease
   - Absence of antibodies and abnormal thyroid function tests does not exclude quiescent disease.
   - Unique physical exam findings:
     - Ophthalmopathy is unique to Graves’ disease.
     - In severe cases of Graves’, a palpable thrill and audible bruit, usually over the upper poles

   Subacute thyroiditis
   - Features that are present in subacute thyroiditis but not Graves:
     - Asymmetry of the gland
     - Tenderness to palpation of the gland
     - Systemic evidence of inflammation
   - Uptake scans can distinguish between Graves and Subacute.
Hashimoto’s thyroiditis

“Hashitoxicosis” can be difficult to distinguish from Graves and requires follow-up
Features that are present in Hashimoto’s but not Graves:
- Goiter is somewhat lobulated, firmer and rubbery compared with that of GD
- Serum levels of thyroid antibodies are generally higher in Hashimoto's disease but may not be helpful in distinguishing individual patients.

2. Know the usefulness of the measurement of T4, free T4, and T3 concentrations in hyperthyroidism

In all cases of hyperthyroidism, except the very rare inappropriate pituitary secretion of TSH, TSH should be undetectable.
T3 may be elevated out of proportion to the T4 because, like TSH, TRAbs stimulate increased T4 to T3 conversion.
Free T4 and T3 are increased.
T3 concentration may be proportionally more elevated than the serum T4 level.
Occasionally, the discrepancy between T4 and T3 levels is exaggerated, with the serum T4 concentration being normal and the serum T3 concentration alone being elevated (T3 thyrotoxicosis).

3. Recognize and identify the various forms of nonthyrotoxic hyperthyroxinemia

Euthyroid hyperthyroxinemia is defined as a condition in which the serum total or, rarely, the free thyroxine (T4) concentrations are abnormal without evidence of clinical thyroid disease.
Changes may be transient or persistent and may be associated with normal, low, or high triiodothyronine (T3) levels.
Because this condition is characterized by a number of different disorders, its true prevalence is unknown.
Familial dysalbuminemic hyperthyroxinemia (FDH)
- Transmitted as an autosomal dominant trait
- Presence of a variant serum albumin with preferential affinity for thyroxine (T4) in clinically euthyroid individuals. Individuals have consistently elevated total T4 and elevated or normal free T4 values with normal TSH levels.
Other disorders that may cause hyperthyroxinemia without thyrotoxicosis
- Peripheral resistance to thyroid hormones
- Some drug-induced conditions associated with non-thyrotoxic elevations of serum thyroxine
  - Amiodarone??

4. Understand that low iodine uptake in the face of negative stimulatory antibodies with high T4, T3, and low TSH may be indicative of a temporary form of hyperthyroidism, such as subacute thyroiditis

Very low values of the RAIU in association with thyrotoxicosis could be due to the presence of factitious thyrotoxicosis, ectopic thyroid tissue, subacute “viral” thyroiditis, toxic multinodular goiter, toxic adenoma, or the thyrotoxic phase of autoimmune thyroiditis (“hashitoxicosis”).
5. Understand that, after the neonatal period, children’s serum T3 concentrations exceed those of adults, and that with normal TSH do not indicate hyperthyroidism, and that obese children may have slightly increased serum T3 concentrations

Serum T3 is low at the time of birth, increases markedly during early infancy, remains high during childhood, and is reduced to adult levels around age 20 years.

Obesity can be associated with mild elevation of TSH and T3, although actually normal in most. The degree of obesity tends to correlate with deviation of hormone levels from average. Weight loss to normal weight normalizes hormone levels in these children.

6. Understand that the reference ranges for thyroid function tests provided by many laboratories are often specific to adults, and not children

Levels of TSH, T3, T4 often higher in children than adults, but most labs report only adult reference ranges.

Table 1. Mean Serum TSH and Free T4 Concentrations at Various Fetal and Postnatal Stages

<table>
<thead>
<tr>
<th>Age</th>
<th>No subjects</th>
<th>Mean serum TSH (mU/L)</th>
<th>Mean serum Free T4 (ng/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midgestation fetus</td>
<td>14</td>
<td>4.5</td>
<td>0.31</td>
</tr>
<tr>
<td>VLBW infants</td>
<td>19</td>
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<td>1.32</td>
</tr>
<tr>
<td>Term infants</td>
<td>43</td>
<td>8.0</td>
<td>1.70</td>
</tr>
<tr>
<td>30-minute TSH surge</td>
<td>22</td>
<td>86</td>
<td>1.70</td>
</tr>
<tr>
<td>3 days</td>
<td>40</td>
<td>6.85</td>
<td>3.72</td>
</tr>
<tr>
<td>10 weeks</td>
<td>43</td>
<td>3.99</td>
<td>1.58</td>
</tr>
<tr>
<td>14 months</td>
<td>79</td>
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<tr>
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<tr>
<td>21–54 years</td>
<td>194</td>
<td>1.87</td>
<td>1.65</td>
</tr>
</tbody>
</table>

*From Thorpe-Beeston et al. (5); mean umbilical cord serum values from published regression analysis.
*bFrom Klein et al. (6); umbilical cord serum.
*cFrom Fisher and Odell (8).
*dIncludes data from Nelson et al. (9).

From Fisher et al. Thyroid 2000.

7. Understand that a mildly increased TSH concentration with normal T4 and T3 concentrations cannot account for excessive weight gain or other symptoms

This is subclinical hypothyroidism, usually only associated with mild, vague, non-specific symptoms, if any.
8. Understand the usefulness of measuring TSH receptor antibodies and the different tests available

Can be helpful as part of complete clinical and biochemical picture for making diagnosis of Graves. See above for types.

c. Treatment

1. Understand the medical management of Graves disease with antithyroid drugs, including dosage, monitoring, and side effects

Most respond well to an antithyroid drugs, and 87-100 % become euthyroid within a few weeks to a few months.

Either methimazole (MMI, 0.1 to 1.0 mg/kg/day or 15-20 mg/m2/day divided daily to TID) or propylthiouracil (PTU, 5 to 10 mg/kg/day or 150-200 mg/m2/day dived every 8 hours) is effective.

The risk of severe PTU-induced liver failure is estimated as 1 in 2000–4000 children. In June 2009 the FDA released a Black Box warning regarding risks of liver failure and death associated with PTU treatment in adult and pediatric patients. Thus, methimazole is preferred treatment.

After normalization of TFTs: can either maintain normal levels 1) by adjusting ATD doses (titrate method) or 2) by giving enough ATD to suppress the gland completely and maintain euthyroidism by thyroxine supplementation (block and replace method). Adding thyroxine to the treatment regimen does not affect the likelihood of sustained remission.

Measure serum free T4 and T3 every four to six weeks initially. If these values are elevated, then increase the dose of methimazole by approximately 0.25 mg/kg increments until thyroid function is normal. TSH can take months to return to normal. Once TFTs normal, can usually decrease dose quickly to ~50% of initial dose for maintainence (if not using block and replace method).

After thyroid function has normalized, follow-up visits, with measurement of serum free T4, T3, and TSH, can be scheduled at three- to four-month intervals.

As patients with hyperthyroidism can have slightly low white blood cell counts and high serum ALT and GGT concentrations, measure baseline CBC and LFTs prior to starting treatment. Recheck CBC in event of fever or during intercurrent illness (esp sore throat). Discontinue therapy if WBC <1500. Neutrophil function usually returns spontaneously after one to two weeks. Re-measure liver enzymes and serum bilirubin in event of clinical evidence of liver disease.

Common side effects – mild elevation of transaminases, mild leukopenia and/or granulocytopenia, rash, pruritis, hives, hair loss, nausea, decreased taste, joint pain, arthralgia.

Severe side effects – agranulocytosis, neutropenia, thrombocytopenia, aplastic anemia, hepatitis, arthritis, vasculitis, cholestatic jaundice, Stevens-Johnsons.

2. Understand the medical management of Graves disease with antithyroid drugs including pharmacologic actions
Methimazole, carbimazole and propylthiouracil inhibit the incorporation of oxidized iodine into the tyrosine residues of thyroglobulin. They also block the coupling of iodotyrosyl residues that form T4 and T3.
PTU also inhibits peripheral deiodination of T4 to T3.
Iodide blocks hormone synthesis and release from the gland transiently.
Glucocorticoids decrease T4 to T3 conversion.

3. Understand the medical management of Graves disease with antithyroid drugs including indication for seeking alternative treatments

Only 30-50% of patients will go into remission with ATDs.
Medication therapy is required for a long time and maybe for a lifetime.
20-30% of patients on drug therapy develop some complication.
ATD complications that require stopping therapy include agranulocytosis, hepatitis, severe arthritis, aplastic anemia or a severe skin reaction.
May also consider alternative therapy if unable to achieve euthyroidism on ATDs or with relapse of GD after remission with ATDs.

4. Know how to use beta-blocking agents for immediate control of the symptoms of Graves disease

Beta blockers ameliorate the symptoms of hyperthyroidism that are caused by increased beta-adrenergic tone, including palpitations, tremulousness, anxiety and heat intolerance.
Propranolol may be dosed in children and adolescents 1-2 mg/kg/day divided every 6 hours.
Propranolol in high doses (above 160 mg/day) also slowly decreases conversion of T4 to T3.
Atenolol (0.5-1.2 mg/kg/day) or metoprolol can also be used and are longer acting. These are also cardioselective and can be used in patients with asthma.

5. Know the indications for surgery to treat Graves disease

Relapse after withdrawal from course of antithyroid drugs (especially repeated).
Very large goiter (studies in adults suggest that individuals with large thyroid glands (greater than 80 g) are unlikely to respond to RAI treatment).
Pharmacologic intolerance.
Pregnant women unable to tolerate pharmacologic therapy.
Coexisting suspicious or malignant thyroid nodule.
Severe eye disease.

6. Know the medical preparation for surgery to treat Graves disease

Goal is euthyroidism prior to surgery.
7-10 days prior to surgery use Lugol’s solution (concentrated inorganic iodine, 3-5 drops or 50-150 mg/dose three times per day for 7-10 days) to block thyroid hormone synthesis and release and to decrease the vascularity of the gland.

7. Know the intra and post-operative complications of surgical treatment of Graves disease
Pain, hypocalcemia due to transient or permanent hypoparathyroidism, recurrent laryngeal nerve palsy or damage, wound infection, keloid formation, bleeding/hematoma.

8. Know the risks of radioactive iodine therapy

Relatively safe. Major adverse effect is hypothyroidism (which is actually intended effect in this case). Rarely: Radiation Thyroiditis – thyroid pain lasting 2-3 weeks and transient worsening of hyperthyroidism due to release of TH stores (unless stores first depleted with thionamide therapy). Steroids may be required in severe cases. Possible worsening of Graves Ophthalmopathy and/or infiltrative dermopathy.

9. Know the indications and use of radioiodine in the treatment of Graves disease

- Recurrent hyperthyroidism after long-term treatment with an antithyroid drug
- Major side effect while receiving an antithyroid drug.
- Generally reserved for patients > 10 years based on observations suggesting that the young thyroid gland may be particularly sensitive to radiation and that young children might therefore have an increased risk for thyroid cancer after radiation exposure.

Controversy exists regarding the optimal dosing regimen of radioiodine to ablate the thyroid gland. Patients have historically been treated with one to three doses of 50 to 200 microCi (1.85-7.4 MBq) of 131-I per gram (estimated) of thyroid tissue divided by the fractional 24-hour 131-I uptake. It may be better to use a higher dose to ensure remission.

In patients with renal failure or on hemodialysis, doses must be reduced significantly. Data does not suggest increase in thyroid cancer or secondary malignancy. No increased incidence of congenital anomalies has been found in offspring of treated patients.

Post ablative hypothyroidism is usually achieved within 1-3 months, but may be delayed. Follow-up thyroid testing should begin at about 1 month post-ablation and then every 4-6 weeks to determine appropriate timing of hormone replacement therapy. There is little evidence that radioactive iodine causes or worsens Graves ophthalmopathy in children or adolescents, as has been described in adults.

10. Know the likelihood of remission with medical management and the duration of therapy required for this to occur

The rate of remission of Graves hyperthyroidism in children and adolescents (defined as the proportion of patients who remain euthyroid for at least six months after discontinuation of antithyroid drug therapy) varies from 25-65% in different series.

Children treated with antithyroid drugs take longer to enter a permanent remission than adults. Many practitioners are willing to use antithyroid drugs for many years until a remission occurs.

Once remission occurs, the relapse rate in children has varied from 3-47%, depending on study. Most relapses occur within one year, but later relapses do occur.


d. Prognosis

1. Understand that stimulatory antibodies may persist for years after treatment in a subset of women with Graves disease, and be unrecognizable if thyroid ablation has occurred, increasing the risk for neonatal hyperthyroidism in their offspring

Thyroid antibodies can cross placenta. All pregnant women with a history of GD (even remote, and even after definitive therapy) need to inform their OB provider. They should have TFTs and TSI/TRAbs checked in 3rd trimester as these can be predictors for development of neonatal graves.