Case 2: Graves Disease

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Summary of the case:

* Safia Ali, 29-years old, female accountant. (Being female and young age is helpful information regarding an autoimmune disease).
* Her mother is known to have Vitiligo for 15 year.

Presenting problems	Clinical examination	Investigation
• Always feels hot • Sweats a lot • Tremor • Weight loss	• BMI • Vital signs • Eye examination • Skin and Hand examination • Neck examination • Upper and lower limb examination	• Blood test; Thyroid hormones level/ Autoantibodies level • Thyroid scan

*** Final diagnosis: Graves Disease**

* Treated by: Propranolol (beta blocker), methimizole (carbimazole)

Definition of Graves Disease:

Graves disease is an autoimmune disease that affects thyroid gland. It is caused by activation of thyroid epithelial cells by **autoantibodies to the TSH receptor that mimic TSH action.**

Signs & Symptoms:

- Fatigue, general weakness
- Warm, moist, fine skin
- Tremors, proximal muscle weakness, easy fatigability
- Palpitations, dyspnea on exertion, chest pain, edema
- Dyspnea
- Increased bowel motility with increased frequency of bowel movements

Signs & Symptoms (cont.):

- Exophthalmos (protruding eyes)
- Polyuria, polydipsia
- Heat intolerance, weight loss despite increase or similar appetite, worsening diabetes control
- Reproductive: Irregular menstrual periods, decreased menstrual volume, gynecomastia, impotence
- Restlessness, anxiety, irritability, insomnia
- Increased BMR
- Goiter

Further questions to ask:

- Any environmental reasons such as hot weather, no air condition etc?
- Any history of fever?
- Is she on any medication?
- Any changes in her diet and calories intake?
- Is she on any dietary regime?
- Any history of excessive exercising?
- Any changes in her appetite?
- Any problems with her swallowing, or digestion?
- Any history of abdominal pain, or diarrhea?
- Any history of changes in her bowel motions, and her stools?
- Any family history of tremor?
- Any other associated symptoms?
- Any chronic diseases in the family?
- Past medical history?
- Social history?

Differential Diagnosis:

1) Always feels hot:

- Increase BMR (due to thyrotoxicosis)
- Feverish
- Problem with heat loss
- Environment
- Problem with heat regulatory centres
- Increase catabolism (cancer)
- Malaria

2) Sweats a lot:

- Increase adrenaline, NE, thyroxin secretion
- To cool her body
- Excessive stimulation of sweat gland
- TB
- Malaria
- Excessive sympathetic stimulation

3) Tremors:

- Nervous system overstimulation
- Anxiety/Nervousness
- Increase secretion of Adrenaline/ NE
- Medication use
- Thyrotoxicosis
- Parkinson
- Familial tremor
- Cerebellar injury

Differential Diagnosis (cont.):

4) Lost body weight:

- Decrease appetite
- Decrease calorie intake
- Digestion problem
- Absorption Problem
- Problem with metabolism
- Excessive exercise
- Anorexia nervosa
- Increase catabolism
- Thyrotoxicosis
- Diarrhea
- Abnormal swallowing

Clinical Examination:

- BMI (usually underweight because of increased BMR)
- Vital signs
- Eye examination (to check if there's exophthalmos and other problems)
- Skin & Hand examination (to see if skin is warm sweaty... etc)
- Neck examination (to see if there's goiter)
- Upper & Lower limb examination

Investigation:

- Blood test: Thyroid hormone level/ Thyroid antibodies
- Thyroid scan

Treatment:

The goal is to reduce levels of thyroid hormones back to normal.

- **Medical treatment:**
  - **Methimazole** (in UK) also called Carbimazole (in US): prevents the thyroid peroxidase enzyme from coupling and iodinating the tyrosine residues on thyroglobulin, hence reducing the production of the thyroid hormones T3 and T4. It must be given for six months to two years, in order to be effective.
  - **Beta-blocker** (such as propranolol): May be used to inhibit the sympathetic nervous system symptoms of tachycardia until the antithyroid treatments start to take effect.

- **Radioactive iodine:**
  Accumulates in the thyroid gland and destroys parenchymal cells, producing a long-term decrease in thyroid hormone levels. Clinical improvement may take 2-3 months.

- **Surgical removal (subtotal thyroidectomy):**
  Indicated for the following:
  - Relapse after medical treatment
  - Drug intolerance
  - Cosmetic reasons
  - Suspected malignancy

Prevention:

Early detection and treatment are the best options in order to prevent complications.

Complications (if not treated):

- Heart disorders: arrhythmias, structural changes, congestive heart failure
- Thyroid storm (emergency)
- Osteoporosis

Revision Questions:

1- Discuss the anatomy and the function of the thyroid gland:

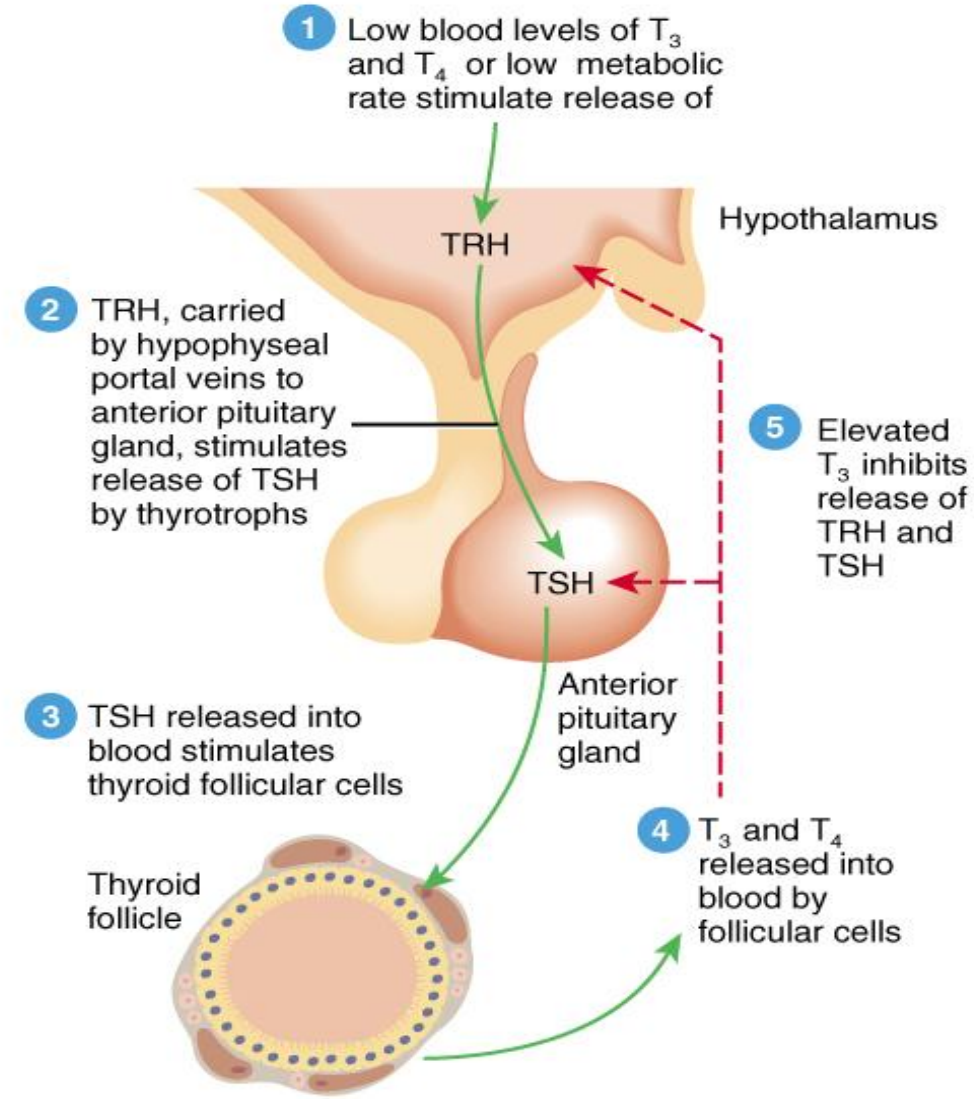
- Anatomy:

Thyroid gland is one of the largest endocrine glands in the body; is located in the front of the neck below thyroid cartilage. It is a butterfly shape gland consisting of two lateral lobes connected by a narrow band called the isthmus. Thyroid gland is related to many important structures, which are in high risk of injury during thyroidectomy. ***External and recurrent laryngeal nerves are the most dangerous structures.***

- Function:

Secretes thyroid hormones (T3 & T4) which virtually act on every organ system in the human body. They increase basal metabolic rate, heat production, and oxygen consumption; and they alter the cardiovascular and respiratory systems to increase blood flow and oxygen delivery to the tissues.

2- Explain the role of feedback mechanisms in the regulation of thyroid hormones:

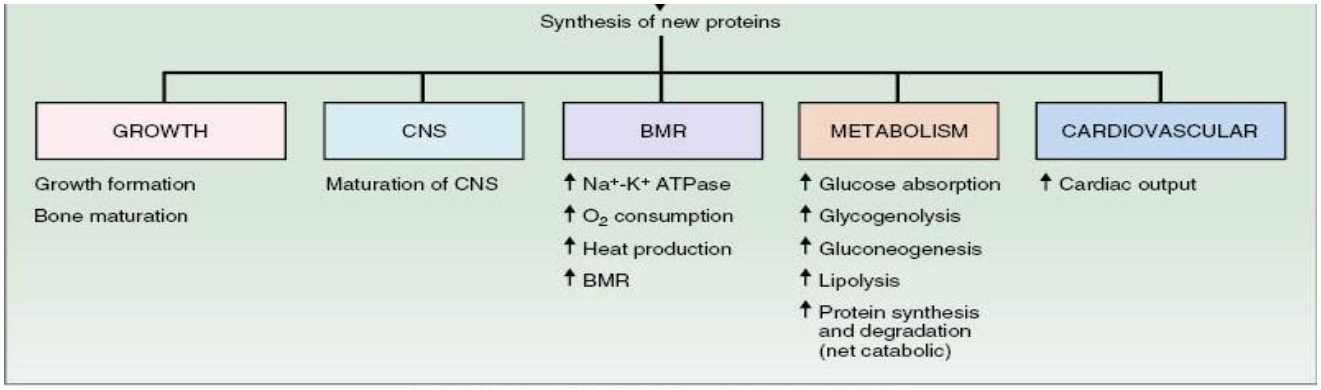


3- Discuss the formation of the thyroid hormones and their physiological actions:

- Steps of formation:

Event	Site	Enzyme	Inhibitor
1 Synthesis of TG; extrusion into follicular lumen	Rough ER, Golgi apparatus		
2 Na^+ - I^- cotransport	Basal membrane		Perchlorate, thiocyanate
3 Oxidation of $I^- \rightarrow I_2$	Apical (luminal) membrane	Peroxidase	PTU
4 Organification of I_2 into MIT and DIT	Apical membrane	Peroxidase	PTU
5 Coupling reaction of MIT and DIT into T_3 and T_4	Apical membrane	Peroxidase	PTU
6 Endocytosis of TG	Apical membrane		
7 Hydrolysis of T_4 and T_3; T_4 and T_3 enter circulation	Lysosomes	Proteases	
8 Deiodination of residual MIT and DIT Recycling of I^- and tyrosine	Intracellular	Deiodinase	

- Physiological actions:



4- Discuss the pathology and pathogenesis of Graves Disease:

Graves disease is an ***autoimmune*** disease that affects thyroid gland. It is the most common cause of endogenous hyperthyroidism characterized by triad of manifestations:

1. ***Thyrotoxicosis***, caused by a ***diffusely enlarged***, hyperfunctional thyroid, is present in all cases.
2. An infiltrative opthalmopathy with resultant ***exophthalmos***
3. A localized, infiltrative dermopathy (sometimes designated ***pretibial myxedema***) is seen in minority of cases.

Graves disease is caused by activation of thyroid epithelial cells by ***autoantibodies to the TSH receptor*** that mimic TSH action. There are also other auto-antibodies involved.

Auto-antibodies to the TSH receptor are:

1. ***Thyroid stimulating immunoglobulin (TSI)***
2. ***Thyroid growth-stimulating immunoglobulin (TGI)***
3. ***TSH-binding inhibitor immunoglobulin (TBII)***

Peak incidence of Graves disease is between ages of 20 and 40, where women are being affected 7 times more commonly than men.

Laboratory features include ***elevations in serum free T3 and T4 and decreased serum TSH.***

5- Discuss the pharmacology of drugs used in Graves disease:

(mentioned earlier)

Learning Objectives:

- Anatomy and functions of pituitary gland
- Discuss the formation of the thyroid hormones and their physiological actions
- Discuss the pathology and pathogenesis of Graves Disease
- Discuss the pharmacology of drugs used in Graves Disease
- Discuss management goals and construct a management plan for a patient with Graves Disease
- Use basic sciences to **interpret the signs, symptoms and investigation results of a patient with Graves disease**:

  In general, an increase in thyroid hormones will cause an increase in the functions that are controlled by them. Thyroid hormones are responsible for synthesizing new proteins, including Na^+-K^+ ATPase, transport proteins, B_1-adrenergic receptors, lysosomal enzymes, proteolytic proteins, and structural proteins. The nature of the protein induced is specific to the target tissue. In most tissues, ***Na^+-K^+ ATPase synthesis*** is induced, which leads to ***increased oxygen consumption, BMR, and heat production***. In myocardial cells, ***Myosin, B1- adrenergic receptors, and Ca+2 ATPase are induced***, accounting for thyroid hormone-induced ***increases in heart rate and contractility***. In liver and adipose tissue, key metabolic enzymes are induced to alterations in carbohydrate, fat, and protein metabolism.

  In Graves **ophthalmopathy (exophthalmos)**, the ***volume*** of the retro-orbital connective tissues and extra-ocular muscles is ***increased*** as a result of several causes:

  1. Marked infiltration of the retro-orbital space by T-cells
  2. Inflammatory edema and swelling of extra-ocular muscles
  3. Accumulation of extracellular matrix components: hydrophilic glycosaminoglycans
  4. Increased number of adipocytes