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EMERGENT SITUATIONS IN ENDOCRINOLOGY

DIABETES INSIPIDUS

- *Disorder resulting from deficient ADH action and is characterized by the passage of copious amounts of very dilute urine*.
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- **A: Central (neurogenic) DI** is due to failure of posterior pituitary to secrete adequate quantities of ADH :
- Hypophysectomy, complete or partial
- Surgery to remove suprasellar tumors
- Idiopathic
- Familial- inherited as autosomal dominant
- Tumors and cysts
- Histiocytosis
- Granulomas
- Interruption of blood supply
- Autoimmune
- Trauma - frequently follows a triphasic course: the initial phase is followed by a phase of anti-diuresis (as ADH is released from damaged axons) and then by the persistent DI.

DIABETES INSIPIDUS

- **B: Nephrogenic diabetes insipidus:**
- Chronic renal disease
- Hypokalemia
- Protein starvation
- Hypercalcemia
- Sickle cell anemia
- Drugs- lithium, fluoride, colchicine, demeclocycline
- Congenital defects
- **Differential diagnosis of polyuria:**
  - Central DI
  - Nephrogenic DI
  - Primary polydypsia (psychogenic, compulsive water drinking)

DIABETES INSIPIDUS

- ***Water deprivation:*** under supervision - patients should be weighed and denied access to water. Healthy individuals will soon reduce urine flow to 0.5 ml/min at concentration greater than of plasma; patients with complete DI will maintain a high urine flow at specific gravity < 1.005 (200 mosm/kg water).
- Patients with psychogenic polydypsia will always increase urine osmolality to a value greater then that in plasma.

- ***Vasopressin test:*** once the diagnosis of DI is established, the ADH-insensitive (nephrogenic) disease must be distinguished from ADH-sensitive (central) form.
- One hour after application of vasopressin, patients with central DI will show increase in urine osmolality > 50%, while patients with nephrogenic DI less than 50%. Patients with primary polydypsia have response less than 9%.

DIABETES INSIPIDUS

- Results of dg. studies in various type of polyuria

	NeurogenicDI	Nephrogenic DI	Psychogenic polyd.
Plasma osmolality	↑	↑	↔ ↓
Urine osmolality	↓	↓	↓
Urine osm during water deprivation	no change	no change	↑
urine osm following Vasopresine	↑	no change	↑
plasma vasopresin	low	normal or high	low

DIABETES INSIPIDUS

- *Treatment*:
- *Central DI*: minirin administered p.o. or intranasaly.
- *Nephrogenic DI:* the underlying disease should be treated if possible
- - diuretic with salt restriction
- - prostaglandin-synthesis inhibitor

HYPOPITUITARISM

- Hypopituitarism is manifested by diminished or absent secretion of one or more pituitary hormones.
- Etiology: invasive - large pituitary tumors, craniopharyngioma, metastatic tumors, carotid aneurysm
- Infiltrative - sarcoidosis, hemochromatosis, histiocytosis X
- Injury - head trauma, child abuse
- Immunologic - lymphocytic histiocytosis
- Iatrogenic - surgery, radiation therapy
- Infectious - mycoses, tuberculosis, syphylis
- Idiopathic - familial
- Isolated

HYPOPITUITARISM

- *Infarction- postpartum necrosis (Sheehan syndrome), pituitary apoplexia*: in
- 1914 Simmonds reported pituitary necrosis in women with severe puerperal sepsis and in 1937 Sheehan published this classic description of its occurrence following post-partum hemorrhage and vascular collapse.
- During pregnancy, the pituitary gland is more sensitive to hypoxemia because of its increased metabolic needs or more susceptible to vasoconstrictive influences because of the hyperestrogenic state.
- More than 75% of gland must be destroyed before clinical manifestations are evident.

HYPOPITUITARISM

- *Spontaneous hemorrhagic infarction of a pituitary tumor (pituitary apoplexy)* frequently results in partial or total pituitary insufficiency.
- Pituitary apoplexy is often a fulminant clinical syndrome manifested by severe headache, visual impairment, ophtalmoplegias, meningismus, and altered level of consciousness.
- Pituitary apoplexy is usually associated with a pituitary tumor, it may be related to diabetes mellitus, radiotherapy or open heart surgery.
- Acute pituitary failure with hypotension, rapid mental deterioration, coma and death may ensue.
- **Emergency treatment** with corticosteroids and transphenoidal decompression of the intracelal contents may be lifesaving and may prevent permanent visual loss.

DISORDERS OF ADRENOCORTICAL INSUFFICIENCY

- Deficient adrenal production of glucocorticoids or mineralocorticoids results in adrenocortical insufficiency, which is either the consequence of destruction or dysfunction of the cortex (primary adrenocortical insufficiency, Addisons disease) or secondary to deficient pituitary ACTH secretion (secondary insuf).

- Clinical features of primary adrenocortical insufficiency
- Weakness, fatigue, anorexia, weight loss 100%
- Hyperpigmentation 92%
- Hypotension 88%
- Gastrointestinal disturbances 56%
- Salt craving 19%
- Postural symptoms 12%

- Acute adrenal crisis represents a state of acute adrenocortical insufficiency and occurs in patients with Addisons disease who are exposed to the stress of infection, trauma, surgery, dehydration, vomiting, salt deprivation, diarrhea.
- *Clinical features:* hypovolemic shock frequently occurs, abdominal pain may mimic acute abdominal emergency. Weakness, apathy and confusion are usual.
- Fever is usual and may be due to infection or to hypoadrenalism per se.
- Additional findings: hyponatremia, hyperkalemia, lymphocytosis, eosinophilia, hypoglycemia.

DISORDERS OF ADRENOCORTICAL INSUFFICIENCY

- Acute adrenal hemorrhage- the usual manifestations are abdominal, flank or back pain and abdominal tenderness.
- Abdominal distension, rigidity and rebound tenderness are less frequent.
- Hypotension, shock, fever, nausea, vomiting, confusion, and disorientation are common, tachycardia and cyanosis are less frequent
- Secondary adrenocortical insufficiency - due to ACTH deficiency, is most commonly a result of exogenous glucocorticoid therapy.
- Pituitary or hypothalamic tumors are the most common causes of naturally occuring pituitary ACTH hyposecretion.

- *Clinical features:* secondary adrenal insufficiency is usually chronic and the manifestation may be non specific.
- Pituitary secretion of ACTH and beta LPH is deficient and hyperpigmentation is therefore not present. Mineralocorticoid secretion is usually normal.
- Volume depletion, dehydratation and hyperkalemia are usually absent.
- Hyponatremia may occur as a result of water retention and inability to excrete a water load but is not accompanied by hyperkalemia.
- Hypoglycemia is occasionally the presenting feature. Acute decompensation with severe hypotension or shock unresponsive to vasopressors may occur.

TREATMENT OF ADRENOCORTICAL INSUFFICIENCY

- *Acute Addisonian crisis :* therapy includes administration of glucocorticoids, correction of dehydration,
- hypovolemia and electrolyte abnormalities, general supportive measures, and treatment of coexisting or precipitating disorders.
- Cortisol in doses of 100 mg i.v. is given every 6 hours for the first 24 hours.
- If improvement occurs and patient is stable, 50 mg every 6 hours is given on the second day, and in most patients the dosage may be then gradually reduced to approximately 10 mg three times daily by the fourth or fifth day.

TREATMENT OF ADRENOCORTICAL INSUFFICIENCY

- In patients with Addisons disease fludrocortisone is added when the total cortisol dosage has been reduced to 50-60mg/d.
- I.v. glucose and saline are administered to correct volume depletion, hypotension and hypoglycemia.

MYXEDEMA COMA

- It is the endstage of untreated hypothyroidism. It is characterized by: progressive weakness, stupor, hypothermia, hypoventilation, hypoglycemia, hyponatremia, water intoxication, shock and death.
- Examination reveals bradycardia and marked hypothermia - body temperature as low as 24° C, yellowish skin, a hoarse voice, a large tongue, thin hair, puffy eyes, ileus, slow reflexes.
- Laboratory clues include: lactenscent serum, high serum carotene, elevated serum cholesterol, increased cerebrospinal fluid protein. Low fT_4 and markedly elevated TSH.
- Thyroidal radioactive iodine uptake is low.
- Pleural, pericardial or abdominal effusion with high protein content may be present.
- ECG shows sinus bradycardia and low voltage.

MYXEDEMA COMA

- Clinical clues to the presence of pituitary myxedema include: a history of amenorrhoe or impotence, scanty pubic or axillary hair, normal serum cholesterol and normal or low TSH levels.

- **Treatment**: pts should be treated in the intensive care unit.
- Blood gases must be monitored regularly and patients usually require mechanical ventilation. Associated illnesses must be treated.
- IV fluids should be administered with caution, and extensive free water intake must be avoided.
- Levothyroxine is administered i.v. - an initial dose of 300-400 µg, followed by 50 µg of levothyroxine i.v. daily.
- If the patient is known to have had normal adrenal function before the coma, adrenal support is probably not necessary. If no data are available, the possibility of adrenal insufficiency exist.
- Full adrenal support should be administered - hydrocortisone 100 mg i.v., followed by 50 mg i.v. every 6 hours, tapering the dose over 7 days.

THYROTOXIC CRISIS (THYROID STORM)

- Ii is the acute exacerbation of all of the symptoms of thyrotoxicosis, often presenting as a syndrome that can be of life-threatening severity.
- Occasionally, thyroid storm may be mild and present simply as an unexplained febrile reaction after thyroid surgery in a patient who has been inadequately prepared.

- More commonly, it occurs in a more severe form after surgery, radioactive iodine therapy, or parturition in a patient with inadequately controlled thyrotoxicosis,
- or during a severe, stressful illness or disorder such as uncontrolled diabetes, trauma, acute infection, severe drug reaction or myocardial infarction.

THYROTOXIC CRISIS (THYROID STORM)

- ***Clinical manifestations***: marked hypermetabolism, excessive adrenergic response.
- Fever ranges from 38 to 41° C, is associated with flushing and sweating, marked tachycardia, often with atrial fibrillation and high pulse pressure and occasionally with heart failure.
- Central nervous system symptoms include marked agitation, restlessness, delirium and coma.
- Gastrointestinal symptoms include nausea, vomiting, diarrhea and jaundice. A fatal outcome will be associated with heart failure and shock.

- Serum levels of T_4 and T_3 are not higher than in patients with thyrotoxicosis.
- In thyrotoxicosis the number of binding sites for catecholamines increases - heart and nerve tissues have increased sensitivity to circulating catecholamines.
- ***Laboratory findings***: elevated serum fT_4, fT_3 and suppressed TSH

THYROTOXIC CRISIS (THYROID STORM)

- **Treatment of thyrotoxic crisis**
- Propranolol 1-2 mg slowly i.v. or 40-80mg orally every 6 hours for controlling of arrhythmias.
- In the presence of severe heart failure or asthma and arrhythmia, cautious i.v. administration of verapamil in a dose of 5-10 mg may be effective.

- Hormone synthesis is blocked by the administration of PTU 250 mg every 6 hours. If the patient is unable to take medication by mouth, methimazole in dose of 25 mg every 6 hours can be given by rectal suppositoria or enema.
- After administration of antithyroid drug, hormone release is retarded by the administration of sodium iodide 1 g i.v. over a 24-hour period, or saturated solution of potassium iodide 10 drops twice per day.

THYROTOXIC CRISIS (THYROID STORM)

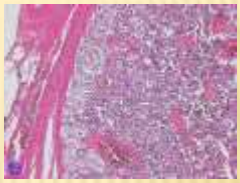
- The conversion of T_4 to T_3 is partially blocked by the combination of propranolol and PTU, administration of hydrocortisone i.v. is additive.
- For controlling of fever acetaminophen is indicated. Aspirin is contraindicated because of its tendency to bind to TBG and displace thyroxine.
- Fluids, electrolyte and nutrition are important. Oxygen, diuretic and digitalis are indicated for heart failure. Finally, it is essential to treat the underlying disease process that may have precipitated the acute exacerbation.
- As an extreme measure to control thyrotoxicosis crisis, plasmapheresis or peritoneal dialysis may be used to remove high levels of circulating thyronins.

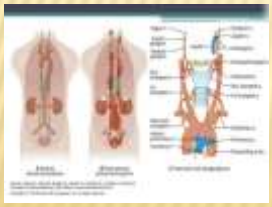
HYPERCALCEMIA

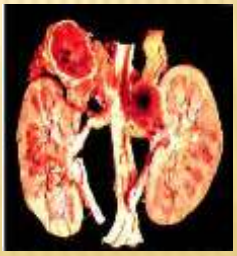
- **Acute severe hypercalcemia (serum calcium > 3,75 mmoUl)** - condition is life-threatening.
- A) Hospitalization - serum calcium, potassium and magnesium must be monitored every 2-3 hours.
- B) Calcium restriction - dietary calcium should be restricted immediately, and all drugs that might cause hypercalcemia (thiazides, vitamin C) should be discontinued.
- C) Reduction of digitalis – if the patient is taking digitalis, it may be wise to reduce the dose because the hypercalcemic patients may be more sensitive to the toxic effect of this drug. Beta adrenergic blocking agents are useful in protecting the heart against the adverse effects of severe hypercalcemia, especially serious arrhythmias.
- D) Hydration and diuretics - the mainstay of therapy is regimen of hydration with saline solutions olus diuresis with furosemide or ethacrynic acid. Furosemide inhibits the tubular reabsorption of calcium and aids the maintaining diuresis. Approximately 4-6 L of isotonic saline should be given i.v. daily, along with 20-100 mg of furosemide i.v. every 1-2 hours or 10-40 mg of ethacrynic acid i.v. every 1-2 hours.
- E) Pottasium and magnesium depletion and dehydration - these complications of therapy must be anticipated and appropriate replacement therapy instituted early.
- IV sodium etidronate and pamidronate and plicamycin.

PHEOCHROMOCYTOMA

- Tumors arising from chromaffin cells in the sympathetic nervous system.
- They release epinephrine or norepinephrine or both, and in some cases dopamine into the circulation.
- In addition they produce a wide variety of active peptides - SMS, substance P, adrenocorticotropin, VIP, interleukin 6, serotonin, gastrin, neurotensin, galanin, insulin-like growth factor, etc.
- Secretion of large amounts of these substances may result in atypical clinical presentation.
- Incidence is about 2/1,000,000.







PHEOCHROMOCYTOMA

- **Common symptoms in pts with hypertension due to pheochromocytoma**
- *Symptoms during or following the paroxysm*
- Headache
- Sweating
- Forceful heartbeat with or without tachycardia
- Anxiety or feeling of impending death
- Tremor
- Fatigue or exhaustion
- Nausea and vomiting
- Abdominal or chest pain
- Visual disturbances
- *Symptoms between paroxysm*
- Increased sweating
- Cold hands and feet
- Weight loss
- Constipation

PHEOCHROMOCYTOMA

- <u>Description of an attack:</u> in patients with paroxysmal release of catecholamines, the symptoms resemble those produced by injections of epi or norepinephrine.
- Episode usually begin with sensation of something happening deep inside the chest, and the stimulus to deeper breathing is noted.
- The patient then becomes aware of a pounding or forceful heartbeat, caused by β1-receptor mediated increase in cardiac output. This throbbing spreads to the rest of the trunk and head, causing headache or pounding sensation in the head.
- The intense α-receptor mediated peripheral vasoconstriction causes cool, moist hands and feet, facial pallor, and marked elevation of blood pressure.
- The decreased heat loss and increased metabolism may cause a rise in temperature or flushing and lead to reflex sweating, which may be profuse and usually follows the cardiovascular effects that begin in the first few seconds after the onset of an attack.

PHEOCHROMOCYTOMA

- Chronic symptoms: intolerance of glucose, increased sweating, weight
- loss, preference of cool room, chronic constriction of the arterial and venous beds leads to a reduction in plasma volume and postural hypotension.

- **Disorders presenting with features of sympathetic discharge or hypermetabolism**
- Angina due to coronary vasospasm
- Severe anxiety states
- Hypertension
- Hypertensive crisis associated with – patraplegia, tabes dorsalis, lead poisoning, acute porphyria
- Menopausal hot flushes
- Autonomic epilepsy
- Thyrotoxicosis
- Hyperdynamic β adrenergic states

PHEOCHROMOCYTOMA

- Tumors may be multicentric in origin, particularly when they are familial or part of the syndromes of MEN and when they are seen in children.
- The incidence of malignant tumors in reported studies varies from less than 5% to more than 10%.
- **Causes of death in patients with unsuspected pheochromocytoma**
- Myocardial infarction
- Cerebrovascular accident
- Arrhythmias
- Irreversible shock
- Renal failure
- Dissecting aortic aneurysm
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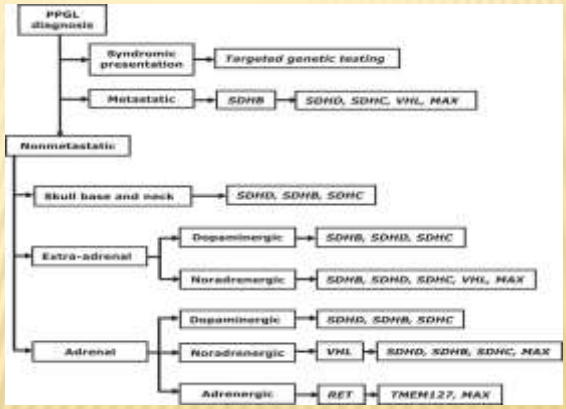
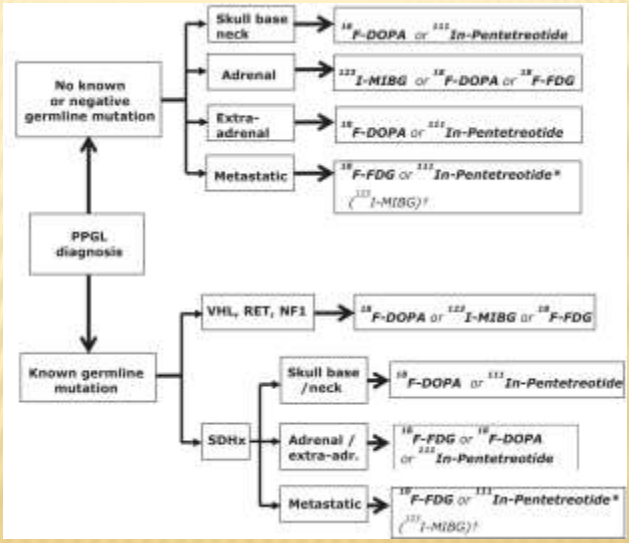
GENETIC IN PHEOCHROMOCYTOMA





Test	Sensitivity (%)	Specificity (%)
Plasma		
Free metanephrines	97-99	82-96
Catecholamines	69-92	72-89
Urine		
Fractionated metanephrine	96-97	45-82
Catecholamines	79-91	75-96
Total metanephrines	60-88	89-97
Vanillylmandelic acid	46-77	86-99
Imaging		
USG abdomen	83-89	30-60
CT abdomen	85-94	29-50
MRI abdomen	93-100	50-100
123I-MIBG	83-100	95-100
18F-DOPA PET	100	100

PHEOCHROMOCYTOMA

- Diagnostic tests and procedures
- Operative exploration for pheochromocytoma should not be done in the absence of chemical confirmation of the diagnosis.
- *Hormone assay:* in patients with continuous hypertension or symptoms, levels of plasma or urine metanephrines and normetamephrines.
- Malignant tumors may release large amounts of dopamine.
- **Localization of tumor**: USG, CT, MRI.
- MIBG scintigraphy and PET/CT with F-DOPA are quite specific for identifying masses producing catecholamines, including neuroblastomas and gangliomas.
- **Treatment:** alfa and betablockers for hypertension
- Resection of tumor
- In malignant ethiology – PRRT with MIBG, LU-DOTATOC, Yttrium DOTATOC, or dibenylin

- End