

NEUROENDOCRINE SYMPTOMS AND DISEASES ASSOCIATED WITH CARCINOID SYNDROME

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BRIEF HISTORY OF CARCINOID

- The term Carcinoid (Karzinoide) was first described in 1907 by pathologist Orbendorffer
- However, the Carcinoid Syndrome was not described until 1954 by Dr. Thorson
- Why the delay?
- To date carcinoid is a diagnosis of exclusion – hallmarked by a varied constellation of symptoms
- Further complicating the diagnostic paradigm is the identification of nearly 40 secretory humoral factors associated with the disease

CARCINOID SYNDROME

- Primarily occurs secondary to the secretion of serotonin, tachykinins, bradykinins, histamine, and prostaglandin
- These vasoactive substances result in systemic symptoms
- Patients experience symptoms based on which of these humoral factors are produced
- This varied secretory pattern makes carcinoid both challenging to treat and diagnose

CARCINOID SYNDROME- 3 GROUPS

- Foregut Carcinoid
 - 30% of patients are symptomatic
 - Intrathoracic, Gastric, 2/3 Duodenal, Bronchial
- Midgut Carcinoid
 - 70% of patients are symptomatic
 - Small intestine, Appendix, Proximal Colon
- Hindgut Carcinoid
 - Rarely symptomatic unless patient has liver mets
 - Distal Colon-Transverse, Descending and Rectum
- Rare
 - Breast, Ovaries, Testes, Middle Ear

BIOCHEMICAL MECHANISM

- Tryptophan Metabolism

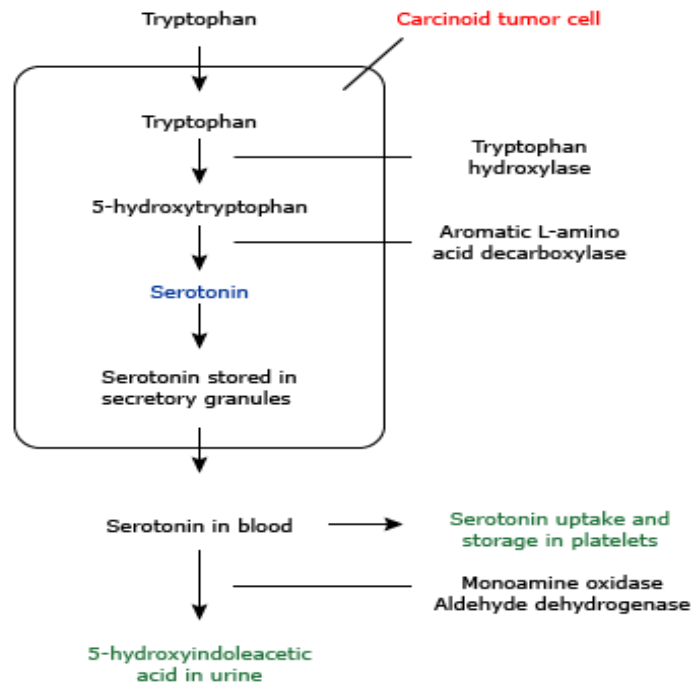
- Altered Tryptophan Metabolism
- Normally 1% of Tryptophan is converted to serotonin
- Tryptophan is an essential amino acid required for niacin production
- In patients with Carcinoid up to 70% is converted to serotonin and its metabolite 5-HIAA
- It is primarily these metabolites that are responsible for the Syndrome

- Variations

- Some hindgut carcinoids cannot convert tryptophan to serotonin
- Therefore, they do not develop carcinoid syndrome
- Some foregut carcinoids cannot convert tryptophan to serotonin and produce histamine instead

***As a result, patients can also develop a tryptophan/niacin deficiency

Tryptophan and serotonin metabolism



Pathways of tryptophan and serotonin metabolism in the carcinoid tumor cell. Patients with the carcinoid syndrome often have increased levels of 5-HIAA excretion in the urine and serotonin in the blood; urinary serotonin excretion is either normal or slightly increased.

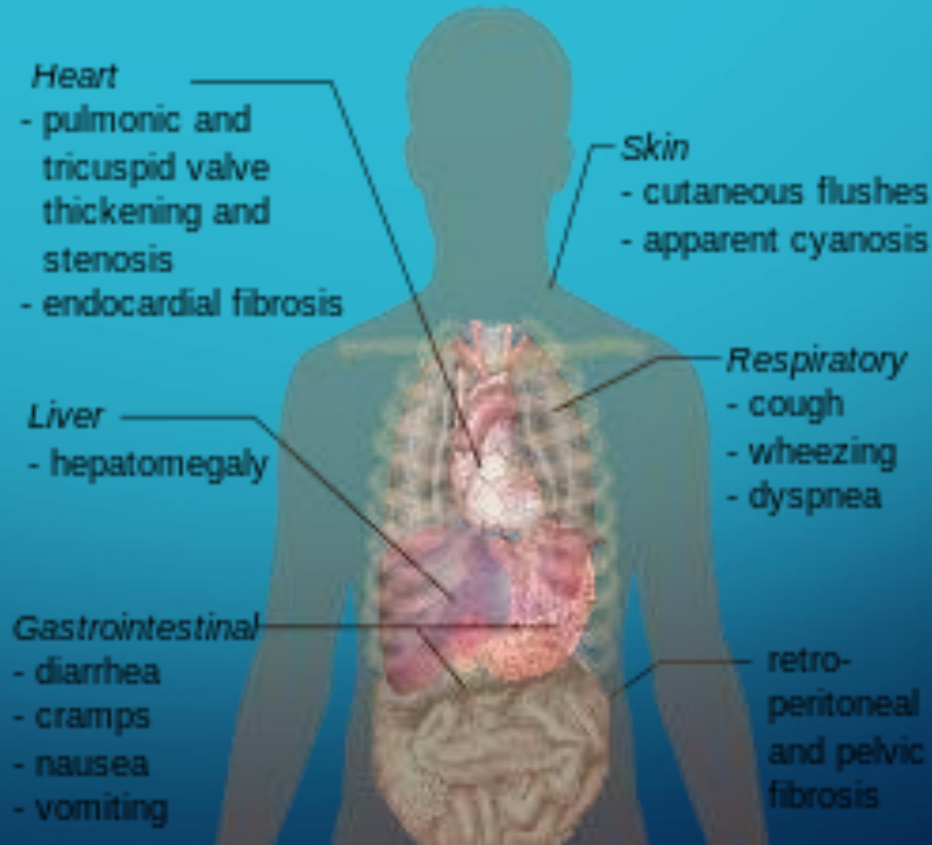
PRIMARY HUMORAL FACTORS

- **Serotonin**- stimulates intestinal secretion and motility, decreasing absorption
→ secretory diarrhea
- **Serotonin**- stimulates fibroblast growth and fibrogenesis → leading to plaque formation and fibrosis- typically cardiac and gastrointestinal
- **Serotonin**- typically involved valves are tricuspid and pulmonic
- **Histamine**- causes flushing, itching and peptic ulcer disease
- **Kallikrein/Bradykinin**- vasodilator → flushing → palpitations → low blood pressure → diarrhea → bronchoconstriction
- **Prostaglandin E, F** - Diarrhea

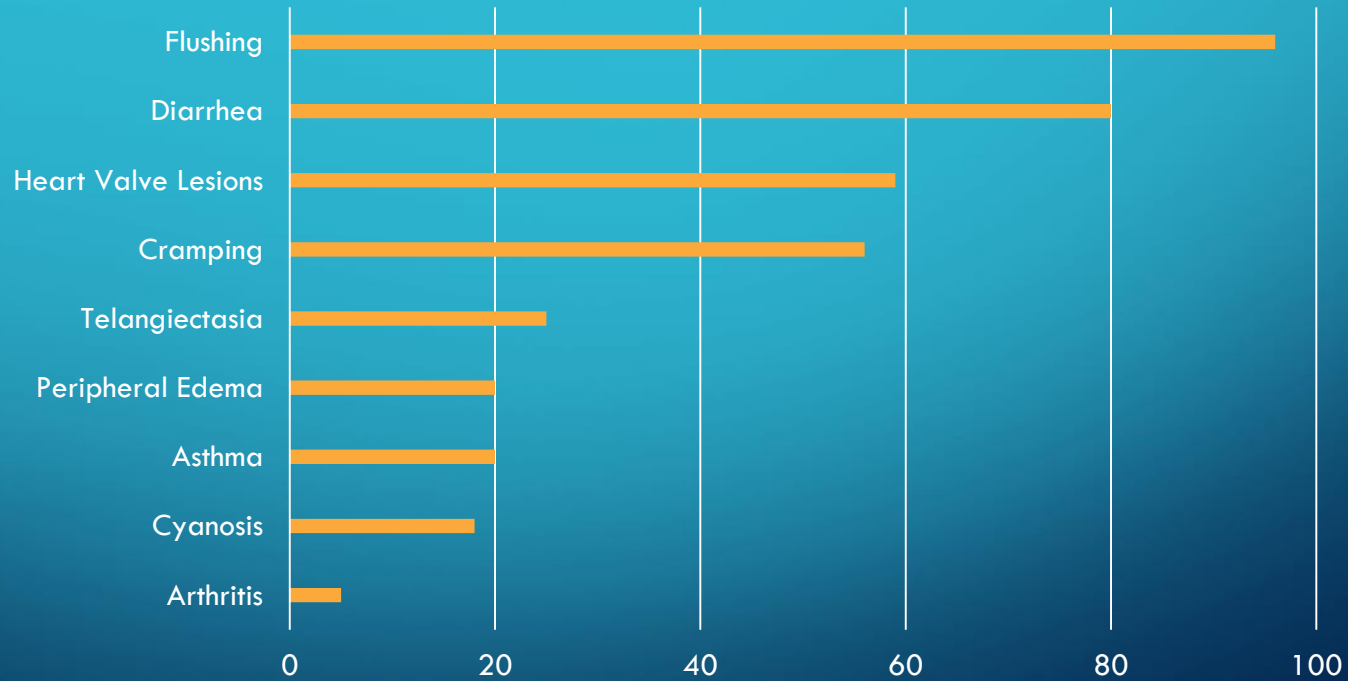
CLINICAL PRESENTATION

- Presentation depends on size, location, and secretory product
- Symptoms can be vague delaying diagnosis for 2-3 years
- Symptomatic Carcinoid Syndrome

Carcinoid syndrome



Carcinoid Presentation in Symptomatic Patients



Cases J.2009 2:78

FLUSHING

- Trigger- can be spontaneous or triggered by a stressor
- Known Triggers- Infection, ETOH, spicy food, emotional or physical stress
- Cause- initially thought to be solely serotonin mediated
 - Research has identified 4 humoral factors
 - Serotonin, Kallikrein, Bradykinin, and Histamine
- Symptoms- Related to the type and concentration of the hormone being secreted

Tests to identify cause of flushing

CLINICAL CONDITION	TESTS
Carcinoid	Urine 5HIAA, 5HTP, SP, CGRP, CGA
Medullary Carcinoma Thyroid	Calcitonin, Calcium Infusion, Ret Proto-oncogene
Pheochromocytoma	Plasma free metanephrines, Urine metanephrines, VMA, Epi, Norepi, glucagon stim, MIBG
Diabetic AN	HRV, 2h PP glucose
Menopause	FSH
Epilepsy	EEG
Panic	Pentagastrin/ACTH
Mastocytosis	Plasma histamine, urine tryptase
Hypomastia, Mitral prolapse	Cardiac echo

CARCINOID FLUSHING- 4 TYPES

- Sudden

- Diffuse, Erythematous- face, neck, upper chest
- Lasts- 1-5 minutes
- Midgut Carcinoids
- Feels Like- sensation of heat and palpitations

- Violaceous

- Diffuse, Erythematous- face, neck, upper chest, facial telangiectasia
- Lasts- 1-5 minutes
- Late Stage Midgut Carcinoids
- Feels Like- No symptoms, patient accustomed to the symptoms- chronic

Carcinoid flush



Marked facial flushing in a patient with the carcinoid syndrome.

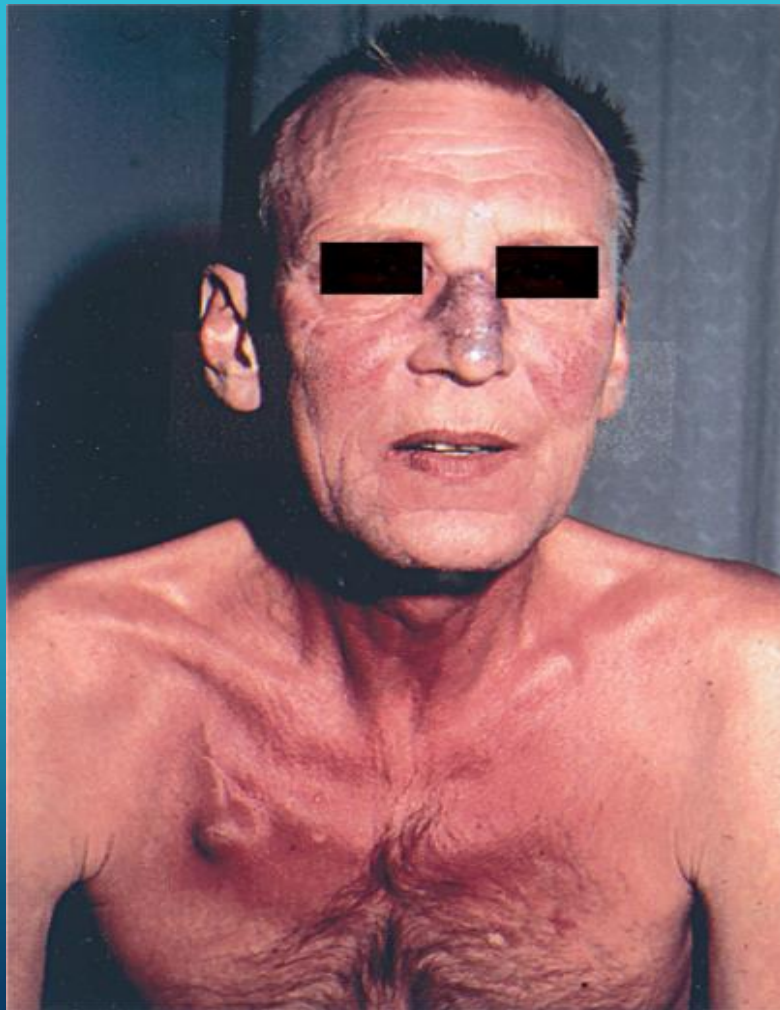
Courtesy of Stephen E Goldfinger, MD.

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Sudden Flush

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Violaceous Flush



CARCINOID FLUSHING- 4 TYPES

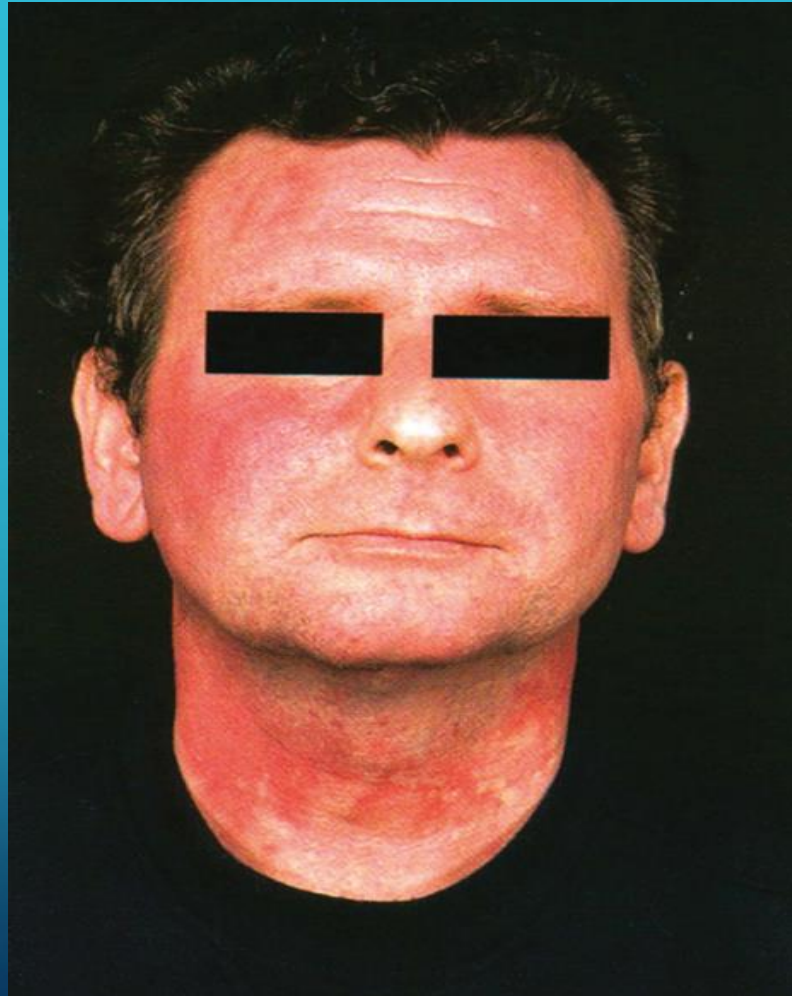
- Prolonged

- Can involve entire body, profuse lacrimation, facial edema, hypotension
- Lasts- hours to days
- Malignant Bronchial Carcinoid
- Feels Like- Excess tear formation, facial swelling, light headed

- Histamine Related

- Patchy bright red lesions, Atypical flushing
- Lasts- minutes
- Gastric Carcinoids- Associated Atrophic Gastritis
- Feels Like- Itchy, sensation of heat

Histamine
Related
Flush



DIARRHEA

- Occurrence- 30-80% of patients
- Primary Cause- Serotonin Mediated
- Associations- Pain and Cramping
- Treatment- Typically good response with serotonin receptor antagonists
 - Octreotide – typically used to control symptoms
 - Ondansetron
 - Ketanserin

CARCINOID HEART DISEASE

- Occurrence- relatively frequent however only 10-20% are symptomatic requiring intervention
- Pathophysiology- collagen deposits in the endothelium affecting blood flow
 - Primarily affects valves- tricuspid and pulmonic → stenosis and regurgitation
 - Right sided lesions- primarily in patients with livers mets
 - Left sided lesions – primarily associated with pulmonary carcinoid
- Cause- serotonin, tachykinins, IGF-I, TGF- β
- Diagnosis- Echocardiogram 70% of lesions identified
- Treatment- Early treatment of carcinoid with somatostatin and interferon analogues

EXTRACARDIAC FIBROTIC COMPLICATIONS

- Intraabdominal Fibrosis

- Resulting in intestinal adhesions
- Commonly see bowel obstruction
- Rarely- bowel ischemia from arterial/venousfibrosis

- Retroperitoneal Fibrosis

- Urethral Obstruction
- Kidney Dysfunction

** As with cardiac fibrosis – established lesions do not resolve or improve with treatment for carcinoid. The goal is prevention of new lesions, and surgical management if indicated

TELANGIECTASIA/PERIPHERAL EDEMA

- **Telangiectasia**

- Permanent venous dilation of blood vessels from chronic flushing/vasodilation, appears as a purple discoloration
- Cause- vasoactive humoral factors
- Typically seen on cheeks, upper lip, and nose

- **Peripheral Edema**

- Swelling in lower extremities
- Cause- as above
- Seen in patients with a history of severe flushing and foregut carcinoid

PULMONARY MANIFESTATIONS

- Occurrence- Rare
- Pathophysiology- bronchial smooth muscle constriction and local edema/swelling
- Cause- secondary to inflammation caused by vasoactive tachykinins and bradykinins
- Diagnosis- Clinical presentation in a patient with known Carcinoid
- Treatment- inhaled bronchodilators

TRYPTOPHAN DEFICIENCY

- Decreased protein synthesis
- Low albumin – low binding proteins
- Nicotinic Acid Deficiency
 - Mental Confusion → Dementia
 - Glossitis- soreness or redness of the tongue.
 - Stomatitis- Inflammation of the mucosa of the mouth and lips
 - Diarrhea
 - Dermatitis- hair loss, red skin lesions
 - Death- rare

BONE COMPLICATIONS

- NET including Carcinoid are associated with a decreased bone Mineral Density (BMD)
- Recent studies indicate a relationship between BMD, serotonin and serotonin metabolites
- 46 carcinoid patients were evaluated – 48.9% male, age 63 +/-10 years
- Carcinoid- gastric, pancreatic, pulm, ovarian
- Elevated urine 5-HIAA were associated with reduce BMD in the hip in all patients

CLINICAL RELEVANCE

- Further studies are needed to evaluate if patients with persistently elevated 5-HIAA levels should be placed on prophylactic medication to protect bone
- Both male and female Carcinoid patients should have a bone density baseline assessment
- We should consider a follow up study if the serotonin and serotonin metabolite levels remain elevated on treatment

CARCINOID CRISIS

- Occurrence- Rare secondary to effective treatment with
 - somatostatin analogues
- Causes- spontaneous, anesthesia, embolization, chemotherapy
 - infection
- Symptoms- severe flushing, diarrhea, hypotension,
 - hyperthermia, tachycardia
- Prevention- iv or sc sandostatin analogues given before and
 - after surgery

*** Patients with pulmonary lesions are most resistant to preventative treatment. They require higher dose octreotide, histamine blockers and IV saline ***

ASSOCIATED CLINICAL SYNDROMES

- Rarely patients with Carcinoid will develop additional Endocrinopathies
- Certain Carcinoid Tumors have the intrinsic ability to auto regulate and release hormones without the involvement of the pituitary gland
- This hormone release leads to the development of clinical syndromes; Cushing Syndrome and Acromegaly are the most common of these rare occurrences
- Prognosis- Ectopic Secretion of these hormones is associated with a more aggressive Carcinoid Tumor
- Aggressive management of these cases is recommended

Neurosecretory cells produce releasing and release inhibiting hormones.

These hormones are secreted into a portal system.

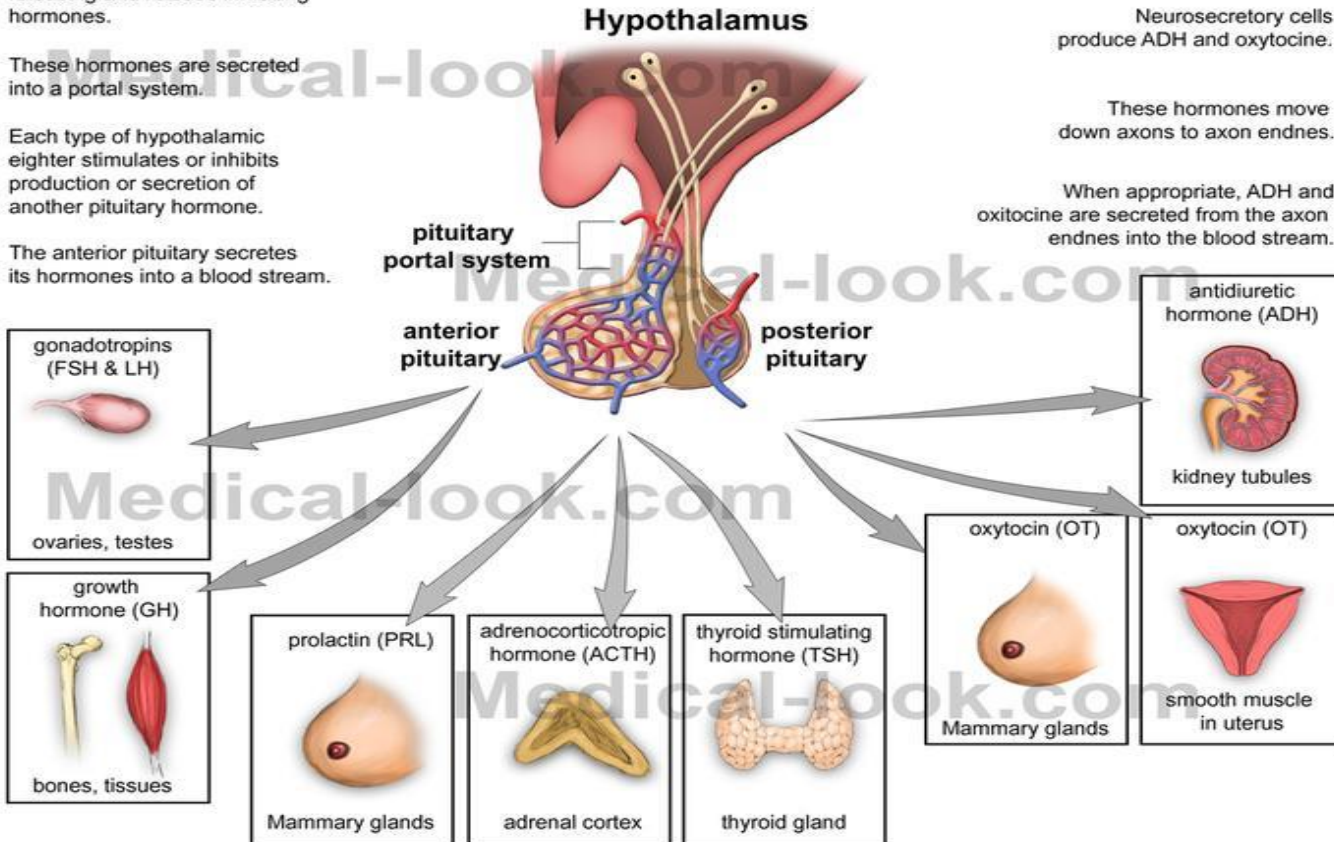
Each type of hypothalamic either stimulates or inhibits production or secretion of another pituitary hormone.

The anterior pituitary secretes its hormones into a blood stream.

Neurosecretory cells produce ADH and oxytocine.

These hormones move down axons to axon endnes.

When appropriate, ADH and oixitocine are secreted from the axon endnes into the blood stream.



CUSHING SYNDROME

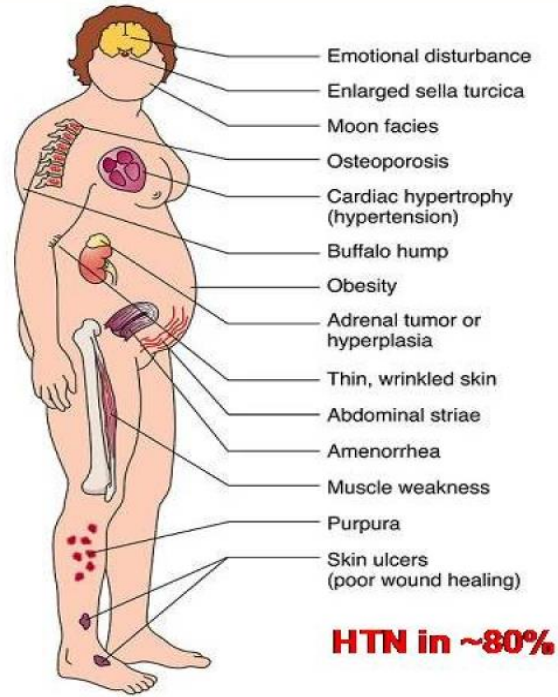
- Carcinoid Associated Cushings- 1% of Cushing cases
- Pulmonic/Thymic Carcinoid- Ectopic Release ACTH, CRH
- Biochemically- stimulates excess cortisol release
- Clinical Presentation
 - unexplained weight gain, weakness, loss of muscle mass, elevated glucose, easy bruising, high blood pressure, purple stretch marks, irregular menses,
 - poor wound healing, emotional lability, moon facies
 - osteoporosis, hypokalemia

Presenting Symptoms & Signs of Cushing's Syndrome

Symptom	Frequency %
Weight Gain	90
Growth Retardation	83
Menstrual Irregularities	81
Hirsutism	81
Obesity (BMI > 85th percentile)	73
Violaceous skin striae	63
Acne	52
Hypertension	51
Fatigue-weakness	45
Precocious puberty	41
Bruising	27
Mental Changes	18
"Delayed" bone age	14
Hyperpigmentation	13
Muscle weakness	13
Acanthosis nigricans	10
"Accelerated" bone age	10
Sleep disturbances	7
Pubertal delay	7
Hypercalcemia	6
Alkalosis	6
Hypokalemia	2
Slipped femoral capital epiphysis	2

Adapted from Magiakou M, Mastorakos G, Oldfield EH, et al. Cushing's Syndrome in Children and Adolescents: Presentation, Diagnosis and Therapy. New England J Med 1994; 331: 820-26.

Signs and symptoms



Normal Appearance



With Cushing's



TREATMENT

- Surgery- Primary Modality of management is localization and surgical resection of the lesion
- Medication
 - Octreotide suppresses release of ACTH/CRH in most cases
 - Cabergoline moderate effect in resistant cases primarily as add on therapy
- Surveillance
 - Regular follow up to assess for recurrence
 - ACTH levels are more accurate than serum cortisol levels

ACROMEGALY

- Definition— Excess growth hormone production resulting in abberent growth of multiple tissues
- Foregut Carcinoid Associated- Ectopic release of IGF-I
- Biochemically- Elevated IGF-I levels result in increased GH (Growth Hormone) levels
- Clinical Presentation
 - Multiple organ complications – See Figure

CLINICAL FEATURES OF ACROMEGALY

- Somatic

- Enlarged Hands and Feet
- Enlarged Heart, CHF, HTN, CM
- Colonic Polyps
- Enlarged jaw/frontal bossing
- Sleep Apnea/Sleep Apnea
- Skin Tags
- Hyperhidrosis
- Carpal Tunnel

- Viceromegaly

- Increased risk of colon cancer
- Increased risk of thyroid cancer

- Endocrine/Metabolic

- Diabetes, Elevated Insulin levels
- Elevated Triglycerides
- Elevated Calcium levels
- Decreased Libido, Impotence, Irregular Menses
- Goiter
- Low Binding Globulin levels

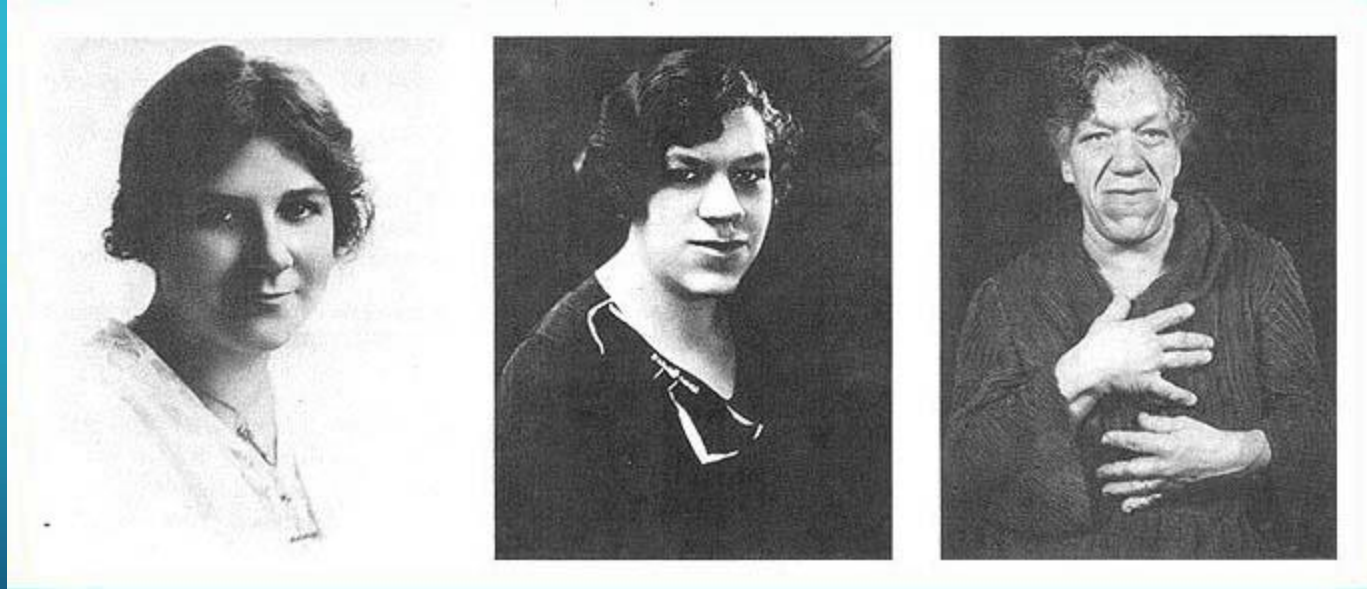
Table 3. Screening of acromegaly complications.

Complications	Evaluation/Diagnostic Tests
Cardiovascular System	BP measurement Electrocardiogram (ECG) Doppler Echocardiogram Doppler ultrasound of the carotids Holter ECG
Respiratory System	Epworth score Polysomnography Cavum MRI
Glucose metabolism	
Non-diabetic	OGTT Fasting insulin (HOMA-IR)
Diabetic	Fasting glucose HbA1c C peptide
Osteoarticular	Clinical evaluation X-ray* Ultrasonography*
Cancer †	Colonoscopy

BP= blood pressure; MRI=magnetic resonance imaging; OGTT= oral glucose tolerance test; HbA1c= hemoglobin A1c.

* If necessary.

† Screening for prostate, breast and female genital tract cancer should follow the recommendations for the general population.



Progression of bone growth in untreated Acromegaly

TREATMENT

- Surgery- Primary Modality of management is localization and surgical resection of the lesion
- Medication- postoperative evaluation of GNRH and GH levels
 - Type I – Postoperative hormone levels very elevated – lifelong suppression with sandostatin
 - Type II – Postoperative hormone levels normal – continue sandostatin until clinically stable
- Surveillance
 - Regular follow up to assess for recurrence
 - Follow GH GNRH levels postoperatively

MEN-I MULTIPLE ENDOCRINE NEOPLASIA

- Genetic Endocrine Disorder associated with Multiple Endocrine Tumors
- MEN-1 is a rare Autosomal Dominant disorder characterized by a predisposition to tumors of the parathyroid glands, anterior pituitary, and pancreatic islet cells
- Carcinoid is seen in 2.6-5% of patients with MEN-I Syndrome
- The majority of cases are Thymic Carcinoid in men
- Women typically have Bronchial Carcinoid
- Smoking increases the risk of development of Carcinoid in the setting of MEN-I

MEN-I AND ZOLLINGER ELLISON

- Zollinger Ellison is a condition associated with excess secretion of gastrin
- Elevated gastrin levels result in the development of multiple peptic ulcers
- In patients with MEN-I syndrome this condition is associated with Gastric Carcinoids

SCREENING FOR CARCINOID IN MEN-1

- Patients with MEN-1 syndrome typically have a strong family history of this disorder
- Genetic screening is available to confirm the diagnosis
- **Thymic Carcinoid**
 - Most common cause of a mediastinal mass in MEN-1
 - Can be seen on chest X- Ray
 - Typically – no secretory product
 - Typically male patient
- **Bronchial Carcinoid**
 - Rare
 - CT is better than chest X-ray
 - Typically- + secretory product
 - Typically female patient

SCREENING FOR CARCINOID IN MEN-I

- Gastric Carcinoid
 - Evaluated Gastrin levels
 - Suspect diagnosis if patient has a known h/o MEN-I with PUD (peptide ulcer disease)
 - Presence of gastric nodules on endoscopy is highly suspicious
 - Biopsy of suspected lesions showing enterochromaffin cell proliferation

MANAGEMENT OF CARCINOID IN MEN-1

- **Thymic Carcinoid**

- CXR for all patients with Diagnosed MEN-1
- Recommend smoking cessation
- If identified surgical resection and serial follow up for recurrence

- **Bronchial Carcinoid**

- CT evaluation better than SRS in a symptomatic patient or + lab screening
- Surgical resection
- Serial follow up for recurrence

- **Gastric Carcinoid**

- **Serial Screening with Gastrin levels**
- Surgical resection of suspected gastric polyps
- If identified surgical resection and serial follow up for recurrence

CONCLUSIONS

- Carcinoid has an unpredictable and varied presentation
- Each patient is as unique as the disease itself
- We have come very far as a medical community however, we have so much more to learn about this perplexing illness
- We will accomplish this goal as a team; with physicians and patients working together

*The most important thing this is to
never stop questioning*

Albert Einstein