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CHICAGO
MEDICINE &
BIOLOGICAL
SCIENCES

“pheochromocytoma”

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MEDICINE

Objectives :

- Discuss the epidemiology and clinical presentation of pheochromocytoma
- Discuss diagnosis and screening methods
- Pheochromocytoma in pregnancy
- Genetic syndromes associated with pheochromocytoma



Clinical history

- 57 y/o M with past medical history of HTN for years controlled with hydrochlorothiazide 25 mg OD. However, in the last 6 months prior to his presentation, he started having fluctuation in his BP which was managed with additional BP medicines including B-Blocker, metoprolol.
- Few days after the new medicines he noticed that his symptoms got worse, and started having frequent episodes of palpitations associated with sweating and headache. The episode usually lasts for 30-45 min. hyperventilation and meditation did not seem to help.
- He denies any sleeping issues and reported being rested in the morning. However, he mentioned periods of awakening with palpitations, sweating and elevated BPs. He also denies any abnormal bowel movements.
- Denies FH with similar presentations. His father had hypertension with no associated symptoms.
- Denies smoking or alcohol abuse. He also denies any recreational drugs abuse



Physical exam

- Generally: a well-appearing male in no acute distress. BP 140/95. HR 100
- Eyes: non-injected sclera.
- ENT: Clear oropharynx. Normal assessment of hearing.
- Neck: No carotid bruits auscultated bilaterally.
- Respiratory: Clear to auscultation bilaterally.
- Cardiovascular: Regular rate and rhythm. No murmurs, rubs, or gallops. No lower extremity edema.
- Abdomen: Positive bowel sounds. Soft, nontender, nondistended.
- Skin: No rash.
- Musculoskeletal: Normal gait and station.
- Lymphatic: No lymphadenopathy in the neck.
Psychiatric: Alert and oriented x3. Appropriate mood/affect



Work ups

BASIC & COMPREHENSIVE			
Glucose, Ser/Plasma	96 *		
Sodium	136		
Potassium, Ser/Plasma	4.6		
Chloride	95		
Carbon Dioxide	24		
Anion Gap	17 ▲		
BUN	24	Ref: 23 - 30 mmol/L	Lab: UCH
Creatinine	1.4		1.1
GFR Estimate (Calc)	52 *		69 *
Calcium	9.9		

Component Name	7/22/2018
WBC	3.3 (L)
RED BLOOD CELL	5.51
HEMOGLOBIN	14.9
HEMATOCRIT	44.7
MCV	81.1
MCH	26.9
MCHC	33.2
RDW	15.2
PLATELET	224

- TSH/Thyroid hormones were normal

7/31/2018 8:38 AM - Interface, Lab

Component	Value	Ref Range & Units
Collection Duration	24	
Urine Volume	2,900	
Norepinephrine	73	15 - 80
Epinephrine, Ur	14	<21
Dopamine	244	65 - 400

Link to Printable Report

[Click here for printable report](#)

7/27/2018 2:25 PM - Interface, Lab

Component	Value	Ref Range & Units
Normetanephrine	1.5 ▲	<0.90 nmol/L
Metanephrine	0.36	<0.50 nmol/L



- What will be the next step in management ?

A) Order CT scan of the abdomen/pelvis w/wo contrast

B) Order MIBG scan because it has high specificity

C) Order adrenal venous sampling

D) I do not know !

- You localized the pheo tumor , what will be the next step ?

A) Start medical therapy and assess patient for surgery

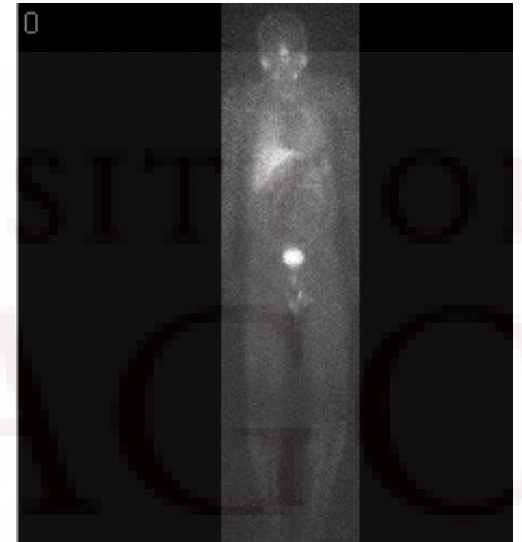
B) Refer patient to surgery immediately

C) Order adrenal venous sampling before surgery

D) Obtain CT- needle guided biopsy to r/o malignancy

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- CT scan of the abdomen and pelvis revealed no evidence of adrenal tumors.
- MIBG scan showed normal radiotracer uptakes.
- MRI abdomen and pelvis revealed no evidence of pheo
- PET neuroendocrine tumor scan (DOTATE) was also negative for pheo



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- Given his typical symptoms and positive biochemical test, we started him on Doxazosin with dose titration gradually to 10 mg BID.
- The patient reported dramatic improvement in his symptoms. The episodes became less in frequency and intensity.
- He also reported no recurring episodes during his sleep.
- Blood pressure has improved to < 130/80 with additional of Amlodipine 5 mg OD.
- He was advised to follow with us annually with a plan to repeat imaging study, CT or MRI every 1-2 years to locate the tumor.



Introduction :

- Endocrine disorders account for 5-10 % of secondary hypertension
- Pheo is a rare cause of hypertension accounts for 0.2 % - 0.6 % of all patients. However, this could be an underestimate as 50% of the tumors were diagnosed at autopsy in one study
- Pheochromocytomas are tumors of the autonomic nervous system, arise from the adrenal medulla and secrete catecholamines and metanephrines.
- Paragangliomas are extra-adrenal ganglia tumors, may or may not secrete hormones- Head and neck tumors.
- Occurs at any age, However, more common in the fourth to fifth decades of life.
- The tumors are sporadic, however, 40% associated with familial disorder..



Clinical presentation:

- Symptoms are present in about 50% of the patients.
- 50% have paroxysmal hypertension while the other 50% have either normal blood pressure or sustained high blood pressure
- The classic triad includes headache (90%), sweating (60%) and tachycardia.
- Less common presentations include orthostatic hypotension, cardiomyopathy, hypertension crisis.
- Abnormalities in the carbohydrate metabolism can occur related to catecholamines excess.
- Most of these tumors 90% are located in the abdomen, mostly intra-adrenal, 10 % bilateral, 10 % malignant.



- Differential Diagnosis for pheochromocytoma by system

CV differential	Endocrinal diff	Neurologic diff	Psychologic diff	Pharmacologic diff
Angina	Carbohydrate intolerance	Hyperadrenergic spells	Factitious	Illegal drug ingestion
Labile essential hypertension	Carcinoid syndrome	Migraine headache	Generalized anxiety disorder	Sympathomimetic ingestion
Orthostatic hypotension	Hyperthyroidism	Postural orthostatic tachycardia syndrome	Hyperventilation Panic attacks	Vancomycin ("red man" syndrome)
Paroxysmal cardiac arrhythmia and torsade de pointes	Hypoglycemia		Somatization disorder	Withdrawal of adrenergic inhibitor Withdrawal of psychotropic medications



Diagnosis and screening

- The diagnosis should be suspected in :
 1. Young adults with hypertension and in any age with new onset- difficult to control BP
 2. Adrenal incidentaloma- both hypertensive and normotensive patients.
 3. Patients with symptoms suggestive of pheo including the classic triad.
 4. Family history of pheochromocytoma
 5. History of familial syndrome that predisposes to pheo.



Diagnosis and screening

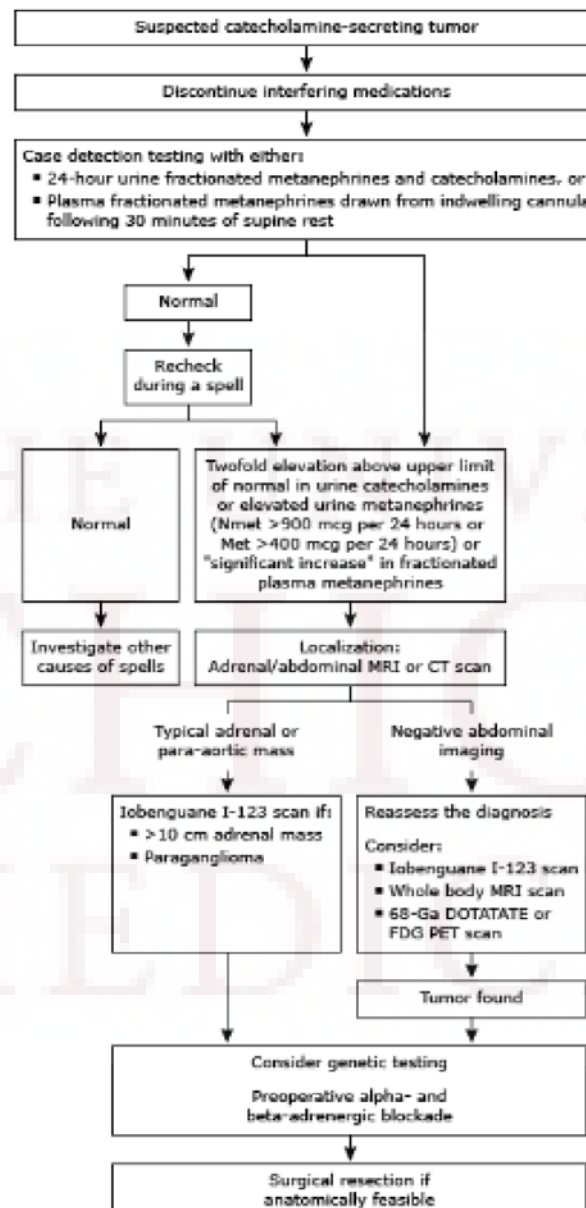
- Once suspected, the screening test can be done in 2 ways :
- The plasma free metanephrines or 24 h urine collection for metanephrines and catecholamines.
- Medications that interfere with screening tests and may yield false positive results.

Medications that may increase measured levels of catecholamines and metanephrines

Tricyclic antidepressants
Levodopa
Drugs containing adrenergic receptor agonists (eg, decongestants)
Amphetamines
Buspirone and most psychoactive agents
Prochlorperazine
Reserpine
Withdrawal from clonidine and other drugs
Ethanol



Continue



Treatment

- Surgery is the treatment of choice because it is curative and relatively safe with complications reported as 0 % to 2 %.
- Laparoscopic approach is the preferred method over open adrenalectomy. However, the latter is usually reserved for very large tumors > 8 cm and extra adrenal paragangliomas.
- The entire gland is removed, however, cortical sparing should be attempted in certain conditions.
- During surgery, it is important NOT to violate the tumor capsule as cells that are spilled can seed the abdominal cavity/adrenal bed and result in tumor recurrence.
- In preparation for surgery, patients should receive preoperative alpha-blockers for 10-14 days.
- During surgery, patients may require IV phentolamine or nicardipine to control BP



Common medications for perioperative blockade

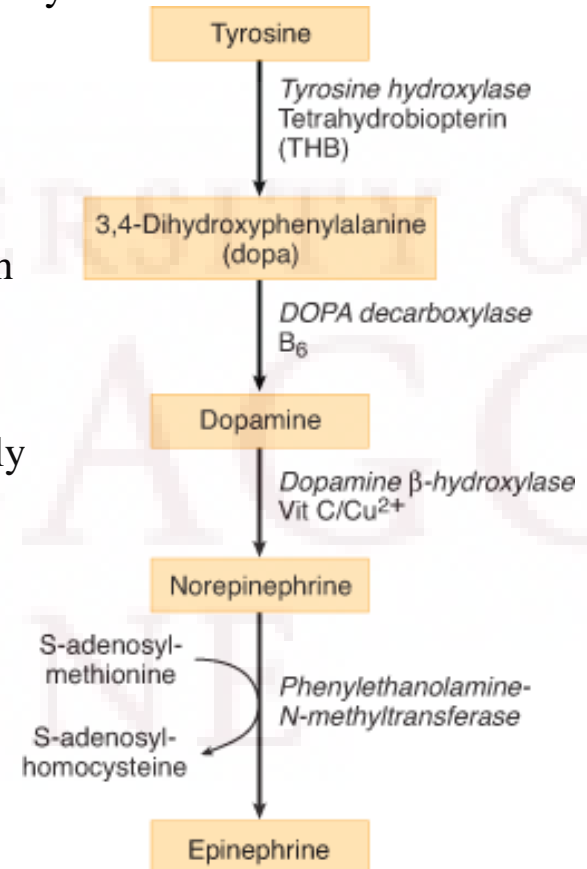
Drug	Action	Characteristics	Dosing	Side effects
Phenoxybenzamine	Nonselective alpha-1 and alpha-2 blocker	Noncompetitive antagonist	10 mg 2-3 daily (maximum 60 mg per day)	Orthostasis, nasal congestion
Doxazosin	Selective alpha-1 blocker	Competitive antagonist	2-4 mg 2-3 x daily	Orthostasis, dizziness
Prazosin	Selective alpha-1 blocker	Competitive antagonist	1-2 mg twice daily	Orthostasis dizziness
Terazosin	Selective alpha-1 blocker	Competitive antagonist	1-4 mg once daily	Orthostasis dizziness
Nicardipine	Calcium channel blocker	Dihydropyridine long acting	30 mg twice daily	Headache, edema, vasodilatation
Amlodipine	Calcium channel blocker	Dihydropyridine long acting	5-10 mg daily	Headache, edema, palpitations
Metyrosine	Tyrosine hydroxylase inhibitor	Decreases catecholamine production	250-500 mg 4 x daily (dose escalated every 2 days)	Severe lethargy, extrapyramidal neurologic side effects and gastrointestinal upset

- Metyrosine is used in some centers in combination with phenoxybenzamine

because the combination may offer CV advantage that has been shown in some studies.

- It can be considered in patients with high CV risk or have high preoperative catecholamines levels.
- The cost for oral capsule 250 mg is around \$36,300 for a supply of 100 capsules, depending on the pharmacy you visit.

Prices are for cash paying customers only and are not valid with insurance plans.



Preoperative Metyrosine Improves Cardiovascular Outcomes for Patients Undergoing Surgery for Pheochromocytoma and Paraganglioma

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ABSTRACT

Background. The goal of preoperative pharmacotherapy for pheochromocytoma (PCC) and paraganglioma (PGL) resection is to minimize intraoperative hemodynamic instability and perioperative cardiovascular complications, but no standard preoperative regimen exists. Historically, treatment used metyrosine and phenoxybenzamine (MP). The recent metyrosine shortage required that phenoxybenzamine alone (PA) be used for treatment. The authors examined their experience to determine the impact of preoperative metyrosine treatment on patient outcomes.

Methods. A retrospective cohort study investigated patients who underwent initial PCC/PGL resection (2000–2014). The primary outcome was intraoperative hemodynamics, measured by heart rate (HR) and systolic blood pressure (SBP). The secondary outcomes included perioperative complications and cardiovascular-specific complications (CVC). Univariate analysis was performed, and adjusted risk differences were estimated after confounding was taken into account.

$p = 0.443$), vasopressors (74.6 vs 87.5 %; $p = 0.120$), and fluid resuscitation (mean, 24.4 vs 24.8 ml/min; $p = 0.761$). Although the perioperative complication rate did not differ significantly between the MP and PA groups (respectively 23.4 vs 34.4 %; $p = 0.198$), the PA patients had a 15.8 % higher rate of CVC even after controlling for confounders ($p = 0.034$). Compared with the MP patients, the PA patients had significantly more hemodynamic instability intraoperatively, with a greater range in HR (7.4 bpm; $p = 0.034$) and SBP (14.8 mmHg; $p = 0.020$).

Conclusions. In this study, preoperative metyrosine improved intraoperative hemodynamic stability and decreased CVC rates in patients undergoing PCC/PGL resection. These data suggest that the addition of preoperative metyrosine may improve operative outcomes.

Pheochromocytomas are rare neuroendocrine tumors arising from chromaffin cells of the neural crest. They typically occur in the adrenal medulla, but in a significant



Follow- up

- All patients should have catecholamines checked 4-6 weeks after surgery
- All patients should have annual plasma metanephrines levels checked for life. Tumors recurrences have been seen 25 years later and all pheos have some metastatic potential.
- All patients should be referred for genetic testing because of higher rate of germline mutations
- No need for follow-up cross-sectional studies in most patients with complete tumor resection.



Pheochromocytoma in pregnancy

- Preoperative blockade is the same as for non-pregnant patients.
- It is usually recommended to proceed to surgery around 18- 22 weeks of pregnancy
- Spontaneous delivery should be avoided- greater risks for mother and baby.
- In patients with genetic predisposition, it is recommended to screen before pregnancy and/or pregnancy is confirmed to avoid late diagnosis and worse outcomes.



Pheochromocytoma in Pregnancy A Case Series and Review

Raymond Oliva, Peter Angelos, Edwin Kaplan, George Bakris

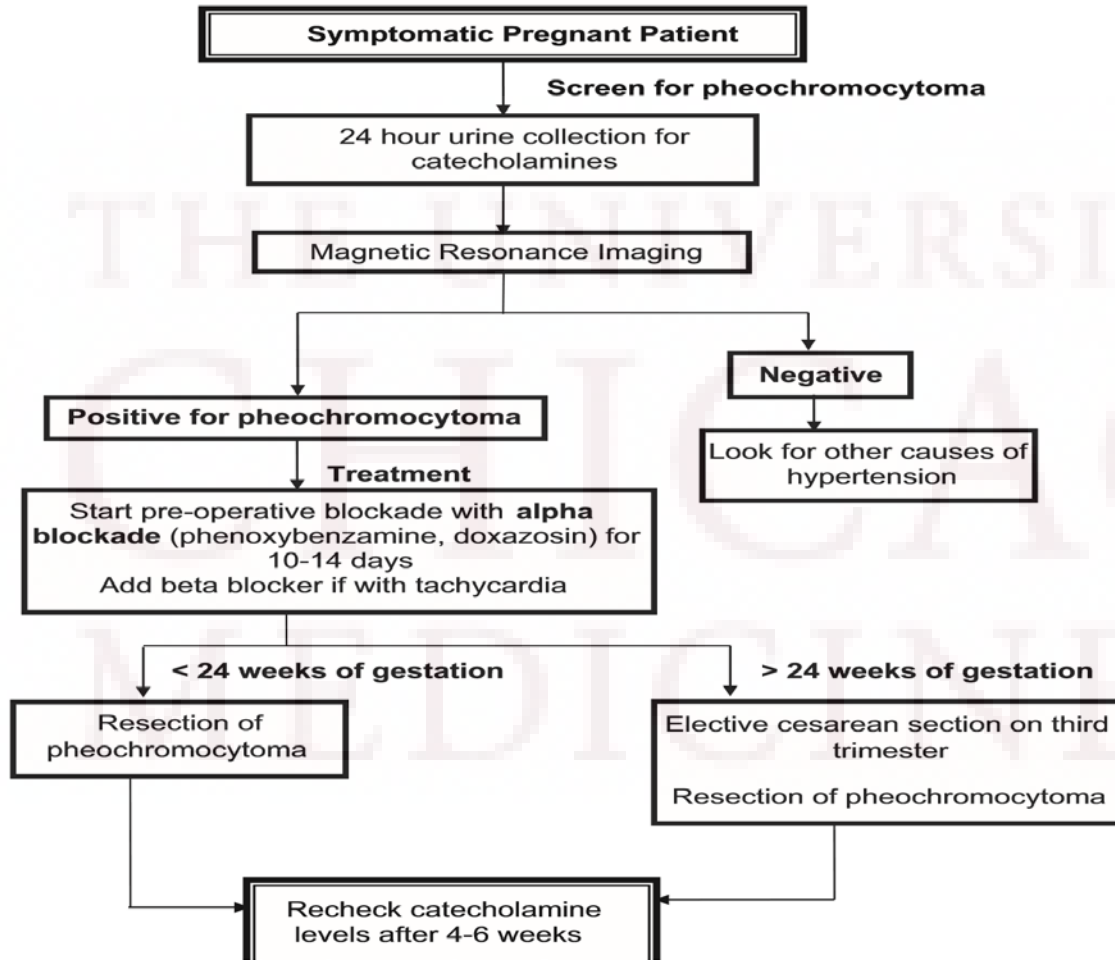
Hypertensive disorders in pregnancy remain among the most understudied areas despite the recent advancement in medical care and management.¹ Although most of this is ascribed to a pregnancy-specific disorder, preeclampsia, there is a paucity of data and few recommendations about another potentially disastrous hypertensive disorder, pheochromocytoma, a catecholamine producing tumor, with a reported incidence of <0.2 per 10 000 pregnancies.² Despite its rarity, untreated pheochromocytomas carry a risk of mortality for both mother and fetus, as high as 58%.³ This may be attributed to several factors, such as the failure to detect the condition because of its extreme rarity, the tendency of these tumors to have varied presentations, and the fact that pregnancy may preclude certain imaging modalities and radioisotope testing.^{2,4,5} The enlarging uterus may also trigger tumor activity, in addition to the tendency for gravidas to undergo operative procedures on short notice.⁶ Thus, it is imperative that physicians who manage patients with pheochromocytoma familiarize themselves with special considerations in relation to pheochromocytoma during pregnancy. Focus should be directed toward understanding the indications of when women with chronic or de novo hypertension during gestation should undergo the special tests used to diagnose pheochromocytoma and how to manage the disease once diagnosed. This report surveys 6 pheochromocytomas managed at our institution, reviews the literature of pheochromocytoma

hypertensive for 7 years and was initially treated with atenolol. She had a history of 2 abortions and symptoms of severe headaches, palpitations, dizziness, and intermittent diaphoresis. Her blood pressure readings varied between highs of 210/120 mm Hg and as low as 80/50 mm Hg when standing. She also had new onset of arrhythmias. Biochemical and imaging testing was positive for an extra adrenal pheochromocytoma and was one of the first cases to use MRI in gestation. She was prescribed 40 mg/d of phenoxybenzamine and 40 mg/d of propranolol. She maintained acceptable blood pressures until gestational week 37, when she underwent cesarean section and an exploratory laparotomy resulting in a successful pregnancy outcome and removal of the tumor.⁷

Case 2

A 21-year-old black female presented to the emergency department with uncontrolled hypertension and elevated blood sugar levels during her 16th week of gestation. She was known to have chronic hypertension and had been treated with labetalol with blood pressures ranging from 160 to 170/80 to 100 mm Hg. She was admitted with an initial diagnosis of preeclampsia. Ultrasound revealed a right adrenal mass measuring 5×4 cm, suggesting the possibility of a pheochromocytoma. Urinary metanephrines measured 4602 $\mu\text{g}/24$ hours (normal [NI]: <900) and normetanephrines 4464





Genetic syndromes

- Up to 40% of patients with pheo and paraganglioma have a germline mutation in one of over 14 genes identified.
- The first syndromes noted to increase the risk of pheo were, neurofibromatosis type 1 , Multiple endocrine neoplasia type 2 and Von Hippel Lindau disease.

Gene	Syndrome	Pheo location
NF1	Neurofibromatosis type 1	Adrenal pheochromocytomas
VHL	von Hippel Lindau	Adrenal pheochromocytomas
RET	Multiple Endocrine Neoplasia type 2	Adrenal pheochromocytomas
SDHA	Hereditary paraganglioma syndrome	Any location
SDHB	Hereditary paraganglioma syndrome	Extraadrenal paraganglioma (any location)
SDHC	Hereditary paraganglioma syndrome	Head and neck paragangliomas (thoracic paragangliomas)
SDHD	Hereditary paraganglioma syndrome	Head and neck paragangliomas (any location)
SDHAF2	Hereditary paraganglioma syndrome	Head and neck paragangliomas
TMEM127	Familial pheochromocytoma/paraganglioma syndrome	Adrenal pheochromocytoma (any location)
MAX	Familial pheochromocytoma/paraganglioma syndrome	Adrenal pheochromocytomas
FH	Hereditary leiomyomatosis and renal cell cancer syndrome	Any location

- Neurofibromatosis type 1 :
- NF1 occurs in 1: 3000 people. It is autosomal dominant syndrome caused by inactivating mutation in the NF1 tumor suppressor gene with end results of uncontrolled cell proliferation.

NF1 is diagnosed clinically if the patient has 2 or more of the following :

- 1- café au lait spots
 - 2- Lisch nodules
 - 3- two or more cutaneous neurofibromas
 - 4- one or more plexiform neurofibroma
 - 5- optic glioma
 - 6- first degree relative with NF1
- Risk of malignancy is 12%.



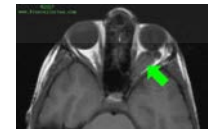
LISCH NODULES



Dermal Neurofibromas



Plexiform Neurofibroma



Multiple Endocrine Neoplasia (MEN) type 2 :

- Autosomal dominant occurs in 1: 30000 people. Caused by activating mutation in RET protooncogene.
- There are 2 subtypes: MEN2A represents 90 % of the cases. Patients at risk for pheochromocytoma, medullary thyroid carcinoma and hyperparathyroidism.
- The guidelines recommend annual screening with biochemical test for pheo beginning at age 11 (high risk mutation) and age 16 (moderate risk mutation).
- The risk of malignancy < 5%.

Von Hippel Lindau Disease :

- Autosomal dominant syndrome occurs in 1 : 36000. caused by inactivating mutation in the VHL gene.
- The syndrome characterized by multiple different tumors and cysts.
- Screening for pheo with biochemical test should start at age 5. 5 % risk of malignancy.



Some facts to remember

- Pheo is a rare cause of secondary hypertension
- Always review medication lists and avoid screening in ill and hospitalized patients- High false positive rates.
- It is not easy to differentiate between benign and malignant tumors. They look the same histologically.
- Avoid B- blockers initially till the patient is adequately alpha blocked.



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