
به نام خدا

Case

دختر 14 ساله

حملات تعریق-تپش قلب-سردرد و تهوع-دل درد

در سونوگرافی توده solid-cystic45در 22 بین کلیه چپ و پانکراس

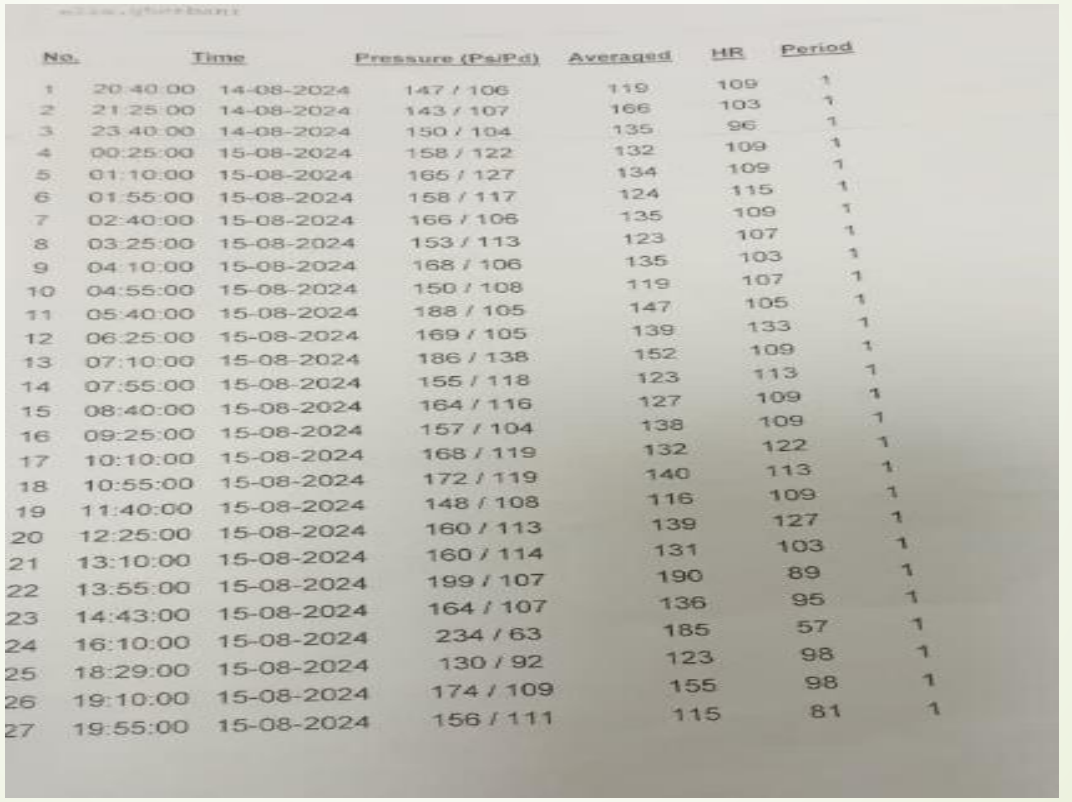
در حین جراحی افزایش فشار خون در حد 26 داشته که جراحی کنسل شده و مشاوره غدد درخواست شد

شرح حال مشابه در دایی بیمار

BP=109/73-وزن 41 کیلوگرم –معاینات طبیعی

Echocardiography: floppy MV-mild LVH

Holter monitoring



No.	Time		Pressure (Ps/Pd)	Averaged	HR	Period
1	20:40:00	14-08-2024	147 / 106	119	109	1
2	21:25:00	14-08-2024	143 / 107	166	103	1
3	23:40:00	14-08-2024	150 / 104	135	96	1
4	00:25:00	15-08-2024	158 / 122	132	109	1
5	01:10:00	15-08-2024	165 / 127	134	109	1
6	01:55:00	15-08-2024	158 / 117	124	115	1
7	02:40:00	15-08-2024	166 / 106	135	109	1
8	03:25:00	15-08-2024	153 / 113	123	107	1
9	04:10:00	15-08-2024	168 / 106	135	103	1
10	04:55:00	15-08-2024	150 / 108	119	107	1
11	05:40:00	15-08-2024	188 / 105	147	105	1
12	06:25:00	15-08-2024	169 / 105	139	133	1
13	07:10:00	15-08-2024	186 / 138	152	109	1
14	07:55:00	15-08-2024	155 / 118	123	113	1
15	08:40:00	15-08-2024	164 / 116	127	109	1
16	09:25:00	15-08-2024	157 / 104	138	109	1
17	10:10:00	15-08-2024	168 / 119	132	122	1
18	10:55:00	15-08-2024	172 / 119	140	113	1
19	11:40:00	15-08-2024	148 / 108	116	109	1
20	12:25:00	15-08-2024	160 / 113	139	127	1
21	13:10:00	15-08-2024	160 / 114	131	103	1
22	13:55:00	15-08-2024	199 / 107	190	89	1
23	14:43:00	15-08-2024	164 / 107	136	95	1
24	16:10:00	15-08-2024	234 / 63	185	57	1
25	18:29:00	15-08-2024	130 / 92	123	98	1
26	19:10:00	15-08-2024	174 / 109	155	98	1
27	19:55:00	15-08-2024	156 / 111	115	81	1

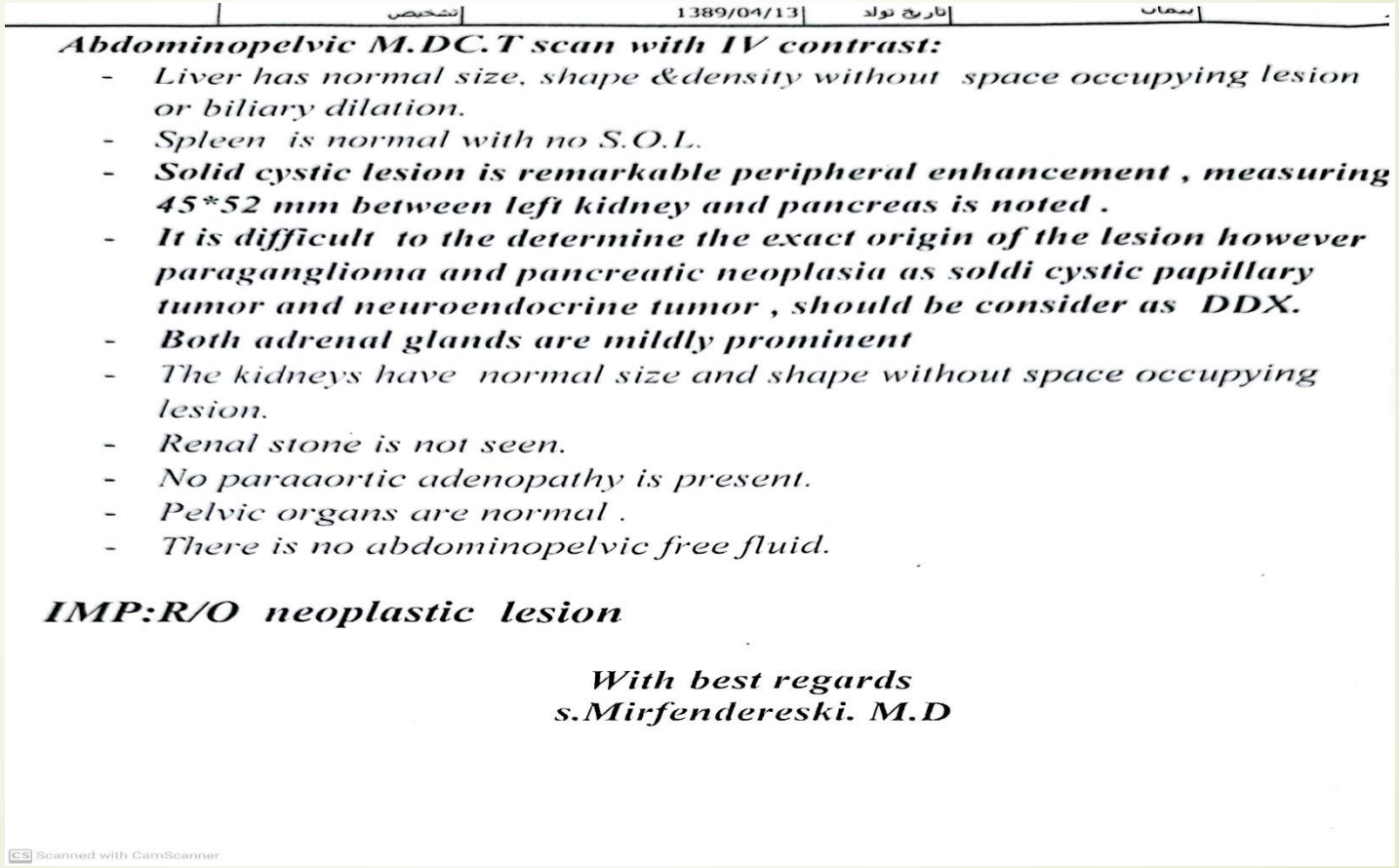
Lab data

- CBC-Na/k-LFT-Bun/cr-Ca/ph: NL
- Urine: Epi:43 < 20
- Nepi :126 <90
- Metanephrine:124 <350
- Normetanephrine:3125 <600

Lab data

- Plasma Metanephrine:8 up to 100
- Plasma Normetanephrine:2689 up to 220

Abdominal CT



تشخیص | 1389/04/13 | تاریخ تولد | بیمار

Abdominopelvic M.DC.T scan with IV contrast:

- Liver has normal size, shape &density without space occupying lesion or biliary dilation.
- Spleen is normal with no S.O.L.
- **Solid cystic lesion is remarkable peripheral enhancement , measuring 45*52 mm between left kidney and pancreas is noted .**
- **It is difficult to the determine the exact origin of the lesion however paraganglioma and pancreatic neoplasia as soldi cystic papillary tumor and neuroendocrine tumor , should be consider as DDX.**
- **Both adrenal glands are mildly prominent**
- The kidneys have normal size and shape without space occupying lesion.
- Renal stone is not seen.
- No paraaortic adenopathy is present.
- Pelvic organs are normal .
- There is no abdominopelvic free fluid.

IMP:R/O neoplastic lesion

With best regards
s.Mirfendereski. M.D

Pheochromocytoma and paraganglioma in children

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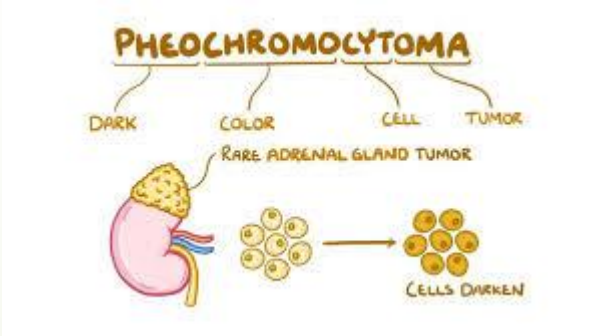
Definition

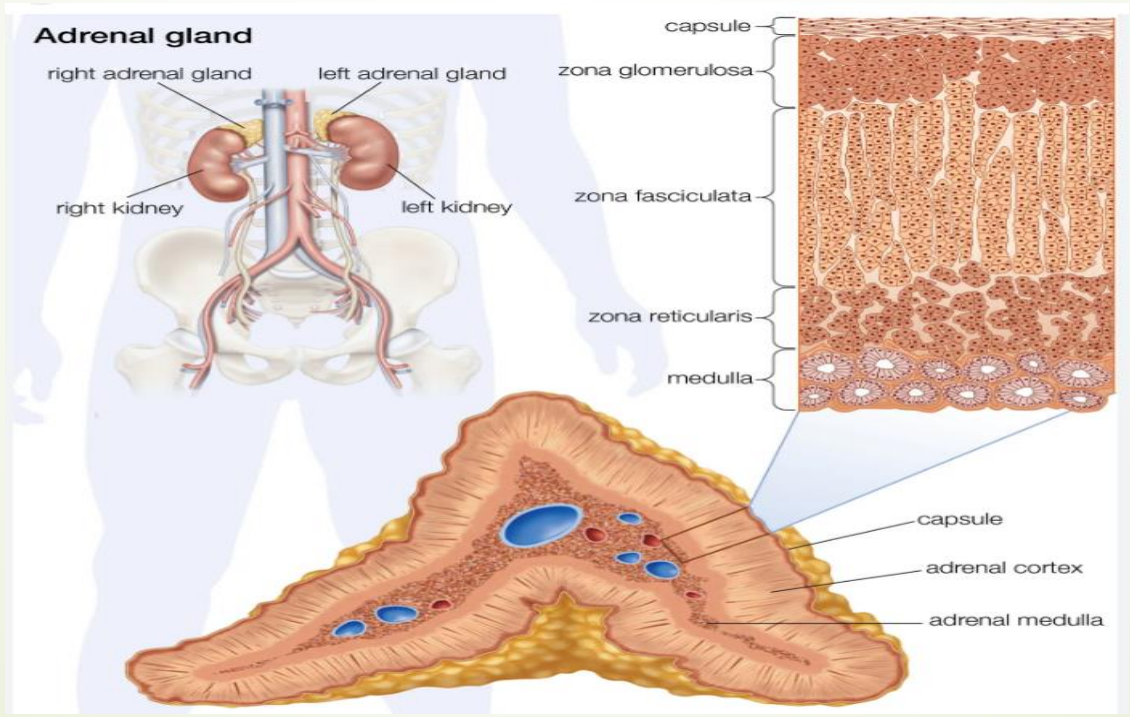
- Pheochromocytomas and paragangliomas are rare tumors in children
- Tumors arise from the adrenal medulla :pheochromocytoma (catecholamines)

- Tumors with extra-adrenal origins :paragangliomas (catecholamines or are nonfunction)



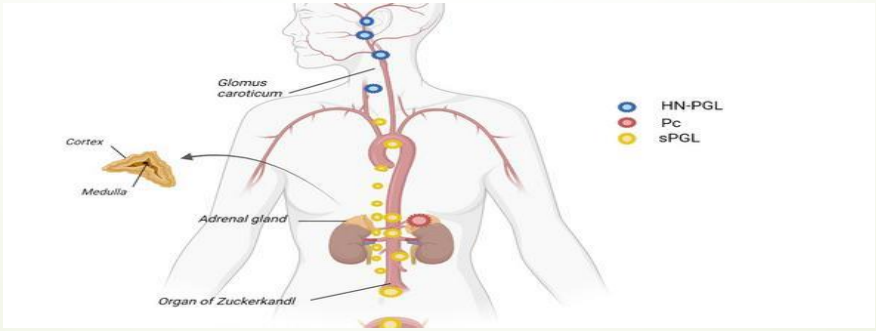
Definition

- Pheochromocytoma :arise from the chromaffin cells of the adrenal medulla
- Greek words phaios (dusky), chroma (color), and cytoma(tumor)



Definition

- Paragangliomas : autonomic nervous system outside of the adrenal medulla
- Sympathetic nervous system (catecholamines)
- Typically are located in the lower mediastinum, abdomen, and pelvis
- Parasympathetic nervous system are usually nonfunctional
- Often located in the skull base, neck, and upper mediastinum

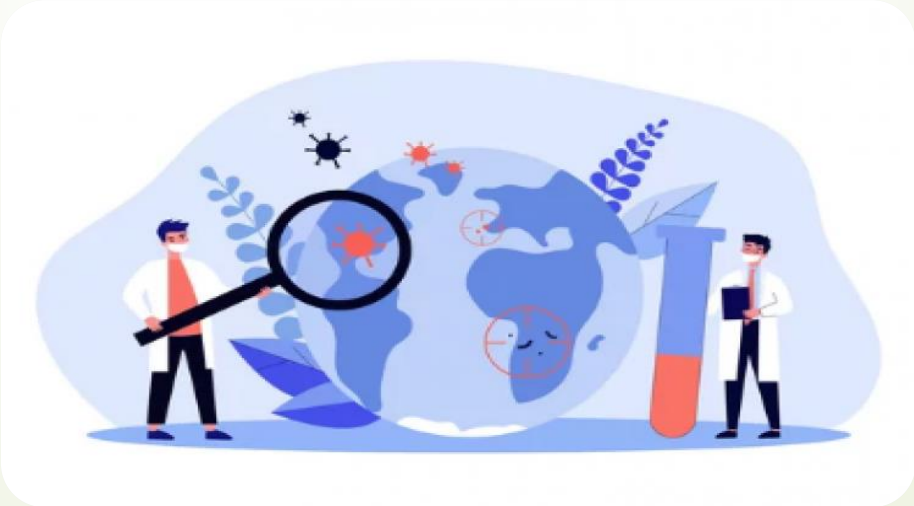


Definition

- The distinction between pheochromocytoma and PGL is an important one because of the implications for :
- Associated neoplasms
- Risk for malignancy
- Implications for genetic testing

EPIDEMIOLOGY

- Incidence rates : 0.3 cases per million per year
- 20 percent of cases diagnosed during childhood
- Among hypertensive children: incidence of surgically confirmed pheochromocytoma or catecholamine-secreting PGL :0.8 to 1.7 percent



EPIDEMIOLOGY

- In adults and children:
- Catecholamine-secreting tumors :80% pheochromocytomas
- 20% paragangliomas
- Because these tumors are uncommon, most pediatric case series are small

EPIDEMIOLOGY

- The largest series included 748 patients with pheochromocytoma or paraganglioma
- 95 (13 percent) presented during childhood
- Compared with adults, pheochromocytoma or paraganglioma in children are more likely to be familial, multicentric , or malignant

PATHOPHYSIOLOGY AND GENETICS

- Pathogenic variants in susceptibility genes :most familial cases of pheochromocytoma or PGL, and also in many apparently sporadic cases

- In one series, nearly 56 percent of pheochromocytoma cases that were initially thought to be sporadic in childhood were due to germline pathogenic variants in susceptibility genes

- When limited to children under age 10: pathogenic variants was as high as 70 to 85 percent

PATHOPHYSIOLOGY AND GENETICS

- It is now imperative:
- All children who present with these disorders, regardless of the family history, undergo germline genetic testing

PATHOPHYSIOLOGY AND GENETICS

- Susceptibility genes are categorized by their biochemical phenotype
- Cluster 1 : noradrenergic phenotype (norEpi and normetanephrine), encoding proteins that function in the cellular response to hypoxia
- Cluster 2 :adrenergic phenotype(Epi and metanephrine), encoding proteins that activate kinase signaling
- Cluster 3 : Wnt signaling pathway

Germline Mutations Associated With Pheochromocytoma and

Syndrome/Name	Gene	Typical Tumor Location and Other Associations
Hypoxic Pathway: Cluster 1[a]		
SDHD mutation (familial paraganglioma type 1)[b]	*SDHD*	PGLs skull base to pelvis; occasionally adrenal medulla; GIST
SDHAF2 mutation (familial paraganglioma type 2)[b]	*SDHAF2*	PGLs skull base to pelvis
SDHC mutation (familial paraganglioma type 3)	*SDHC*	PGLs skull base to pelvis; GIST
SDHB mutation (familial paraganglioma type 4)	*SDHB*	PGLs skull base to pelvis; rarely adrenal medulla; GIST; renal cell carcinoma
SDHA mutation	*SDHA*	Decreased penetrance; PGLs skull base to pelvis; GIST
von Hippel-Lindau (VHL) disease	*VHL*	Adrenal medulla, frequently bilateral; occasionally PGL that may be localized from skull base to pelvis; see text for VHL-associated findings
Hereditary leiomyomatosis and renal cell carcinoma (Reed syndrome)—fumarate hydratase mutation	*FH*	Multifocal and metastatic; associated with hereditary leiomyomatosis, uterine fibroids, and renal cell cancer
Hypoxia-inducible factor (HIF) 2α	*EPAS1*	PGL, polycythemia, and rarely somatostatinoma
Familial erythrocytosis associated with mutation in prolyl hydroxylase isoform 1 (PDH1)	*EGLN2*	Polycythemia associated with pheochromocytoma and PGL
Familial erythrocytosis associated with mutation in prolyl hydroxylase isoform 2 (PDH2)	*EGLN1*	Polycythemia associated with pheochromocytoma and PGL
KIF1B	*KIF1B*	Neuroblastoma
Kinase Signaling Pathway: Cluster 2[c]		
MEN2A and MEN2B	*RET*	Adrenal medulla, frequently bilateral; see text for MEN2A and MEN2B associated findings
Neurofibromatosis type 1 (NF1)	*NF1*	Adrenal or periadrenal PGL; see text for NF1 associated findings
MAX	*MAX*	Adrenal medulla
Familial pheochromocytoma	*TMEM127*	Adrenal medulla; possible renal cell carcinoma

Sporadic tumors

- Approximately two-thirds of pheochromocytomas and PGL in children have no family history of disease
- In patients with apparently sporadic :up to 56 percent will have unsuspected germline pathogenic variants of the RET protooncogene, VHL, SDHD, SDHB, SDHC, SDHAF2, SDHA, TMEM127, or MAX genes
- Genetic testing of these patients may identify individuals and families at risk for other associated tumors

	Children	Adult
Recurrent	29.5	14.2
Hereditary	80.4	52.6
Multifocal	32.6	13.5
Metastatic	49.5	29.1
Cluster1 gene	76.1	39.3

Familial pheochromocytoma

- Syndromic : All of which have AD inheritance
- Von Hippel-Lindau syndrome (VHL) : Associated with pathogenic variants in the VHL tumor suppressor gene
- Between 10 and 20 percent of patients with VHL :pheochromocytoma or PGL
- MEN2A or 2B: Associated with pathogenic variants in the RET protooncogene
- Approximately 50 percent :include pheochromocytoma

Familial pheochromocytoma

- Neurofibromatosis type 1 (NF1) : Due to pathogenic variants in the NF1
- Approximately 3 percent of patients : catecholamine-secreting tumors(pheochromocytomas or abdominal PGL)

Nonsyndromic

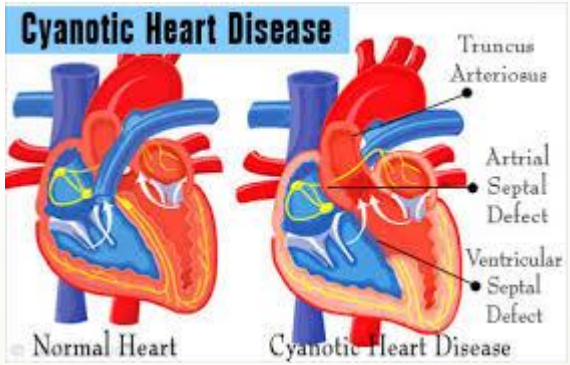
- Familial pheochromocytoma has also been associated with nonsyndromic disease, due to pathogenic variants in
- MAX, TMEM127
- occasionally SDHD or SDHB

Familial pheochromocytoma

- Paragangliomas often arise as a familial disorder with AD inheritance
- The tumors are located most often in the skull base and neck, but also in the thorax, abdomen, pelvis, and urinary bladder
- Most cases are caused by pathogenic variants in the succinate dehydrogenase (SDH) subunit genes (SDHA, SDHAF2, SDHB, SDHC, and SDHD, collectively known as SDHx)
- High rates of multicentric, recurrent, and malignant disease

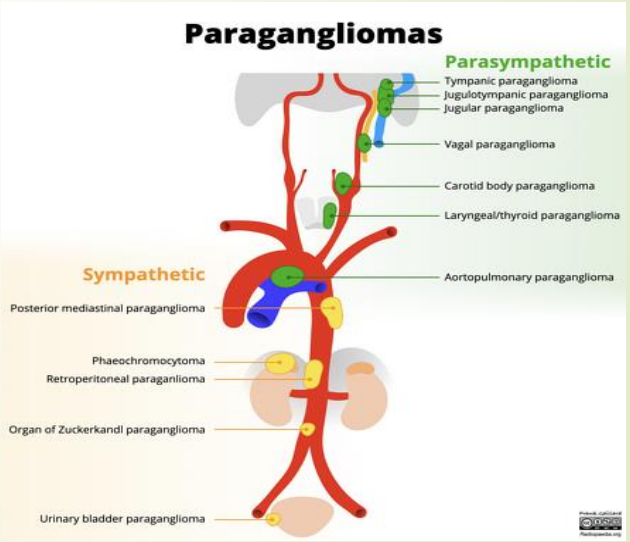
Cyanotic congenital heart disease

- The association between cyanotic congenital heart disease and pheochromocytoma/PGL has been recognized for more than 50 years



TUMOR CHARACTERISTICS

- Tumor location:
- Pheochromocytomas : adrenal medulla
- Catecholamine-secreting paragangliomas are often located in the superior and inferior para-aortic areas (75 percent of extra-adrenal tumors)
- Bladder (10 percent)
- Thorax (10 percent)
- Skull base, neck, and pelvis (5 percent)



TUMOR CHARACTERISTICS

- Compared with adults, children with catecholamine-secreting tumors have a higher incidence of familial disease, bilateral adrenal tumors, extra-adrenal tumors (PGL), and multiple tumors
- Extra-adrenal tumors have been described in 30 to 66 percent of children (10 to 15 percent of adults)
- Multiple tumors have been described in up to 40 percent (5 to 13 percent in adults)

TUMOR CHARACTERISTICS

- Multicentric disease is more common :
- Familial disorders such as MEN2, VHL
- Those with pathogenic variants in succinate dehydrogenase (SDH) and subunit genes (SDHB, SDHC, SDHD, SDHAF2, and SDHA)

Malignant disease

- Children and adolescents are at risk for malignant disease, and this risk may be higher than in adults
- Two observational studies with long-term follow-up reported:
- 50 percent of children had malignant/metastatic disease compared with approximately 30 percent in adults

- The increased rate of malignancy among children was largely explained by their higher rate of cluster 1 pathogenic variants, especially SDHB and VHL

Malignant disease

- Among the pediatric patients:
- One-quarter of the patients with malignant disease had metastases at presentation
- The remainder developed metastases during follow-up

Malignant disease

- In a series of 30 children with these tumors, statistically significant risk factors for malignancy :
- Paraganglioma
- Apparent sporadic disease
- Tumor size greater than 6 cm

Malignant disease

- Malignancy is less common (<5 percent) in individuals with pheochromocytomas or paragangliomas associated with MEN2 or NF1 syndromes

- The risk for patients with VHL syndrome or VHL pathogenic variants is probably intermediate (approximately 10 percent)

Malignant disease

- Malignant pheochromocytomas and PGL are histologically and biochemically the same as benign tumors
- The only clue to the presence of a malignant pheochromocytoma is regional invasion or distant metastases, which may occur as long as 50 years after resection
- Thus, lifelong follow-up is important for any patient with a catecholamine-secreting tumor and particularly for children

CLINICAL PRESENTATION

- The signs and symptoms of pheochromocytomas and PGL are caused by:
- Hypersecretion of norEpi, Epi, and dopamine
- The classic triad :episodic headache, sweating, and tachycardia, usually accompanied by HTN

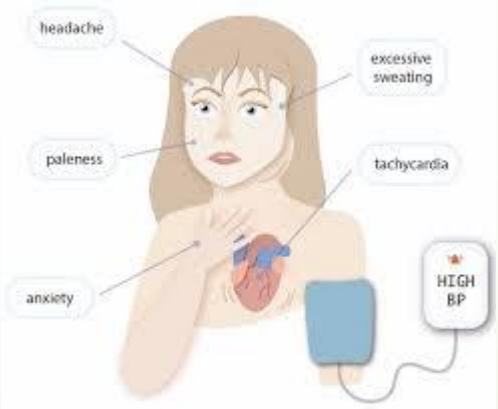
- Less than 50 percent of adult patients have one or more of these three classic symptoms

CLINICAL PRESENTATION

- Presenting symptoms in children are similar to adults, but the frequency is not well defined(case series are small)
- HTN : 60 to 90 %
- HTN is typically sustained but may be paroxysmal
- Malignant HTN can occur with its associated complications (↑ ICP and encephalopathy)

CLINICAL PRESENTATION

- Episodic sweating, tachycardia, or palpitations : 50 to 60 %
- Headache : 50 to 80 %
- The headache may be mild or severe and either episodic or unrelenting



CLINICAL PRESENTATION

- Abdominal pain or distension or back pain : 30 percent in one series
- These symptoms are due to mass effect of the tumor

CLINICAL PRESENTATION

- Other symptoms and signs that occur less frequently :
- Panic attacks or other psychiatric disorders
- Orthostatic hypotension
- Pallor
- Constipation
- Blurred vision
- Papilledema
- Weight loss
- Polyuria
- Polydipsia
- Hematuria
- Dilated CMP

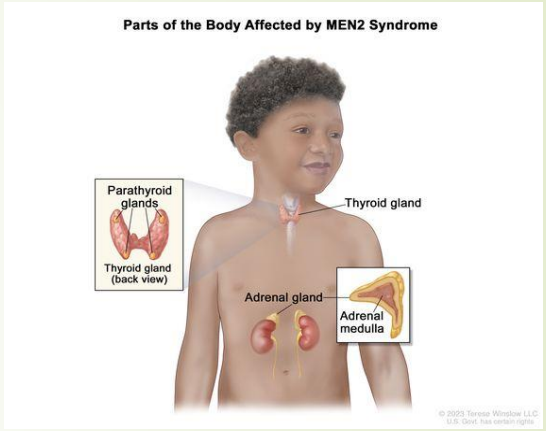
CLINICAL PRESENTATION

- Importantly, ADHD is more common in children with pheochromocytoma and PGL than in the general population

- In pediatric patients with HTN and ADHD :evaluation to rule out pheochromocytoma or PGL is warranted prior to treatment with stimulant medications , which may exacerbate hypertensive crises

CLINICAL PRESENTATION

- Pheochromocytoma associated MEN2
- Approximately one-half of patients are asymptomatic
- Only one-third have HTN



- Pheochromocytoma associated with VHL:
- Approximately 35 percent of patients are asymptomatic and have normal BP and normal catecholamine tests

CLINICAL PRESENTATION

- It is unclear whether the high proportion of asymptomatic patients is due to ascertainment bias due to routine screening for pheochromocytomas in families with MEN2 or VHL
- versus a real difference in the clinical expression of the disease in these familial syndromes

Laboratory tests

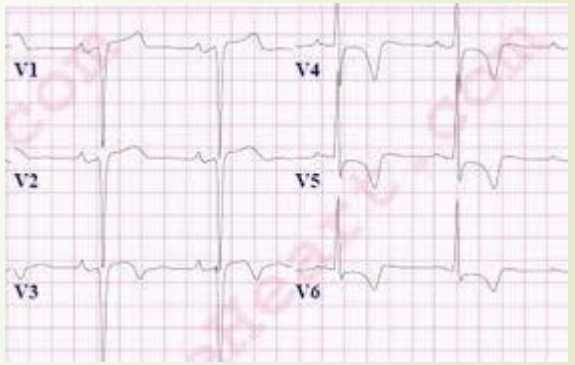
- Patients with PCC or PGL typically have normal results of routine laboratory tests
- ESR or CRP may be elevated(↑catecholamines)
- Approximately 40 percent of adult patients have hyperglycemia
- Hyperglycemia is less common in children

Laboratory tests

- Abdominal or kidney ultrasound have very low sensitivity for detecting pheochromocytomas
- Large tumors are occasionally discovered during a routine evaluation for secondary HTN

Cardiac tests

- Abnormalities of cardiac tests are common in symptomatic adult patients
- ECG : In a small series of adults with pheochromocytoma, three-quarters of whom were symptomatic at presentation
- Normal (53 percent)
- LVH (33 percent)
- Sinus tachycardia (8.3 percent)
- Ischemic pattern (3 percent)
- Supraventricular tachycardia (3 percent)

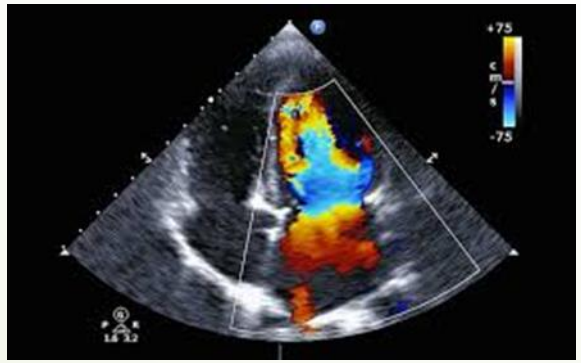


Cardiac tests

- Echocardiogram :is indicated in symptomatic patients
- Echocardiogram is usually normal in asymptomatic patients
- Including those with asymptomatic HTN
- Echocardiographic findings : normal (62.1 percent)
- Concentric LV hypertrophy with normal LV systolic function (27.6 percent)

Cardiac tests

- LV systolic dysfunction (10.3 percent)
- Three symptomatic patients had catecholamine cardiomyopathy with transient LV dysfunction



Approach to evaluation

- The sequence of diagnostic testing depends on whether the patient is being evaluated
- For a catecholamine-secreting tumor
- Clinical symptoms
- Personal or family history of a syndrome or gene pathogenic variant that is associated with these tumors

Patients with symptoms

- For a child presenting with symptoms of sympathetic overactivity, the first step :
- History and physical examination to determine the level of suspicion for a catecholamine-secreting tumor and exclude other causes of the symptoms, such as hyperthyroidism

History

- Sympathetic activity is increased in several conditions
- The two main causes in children are:
- Sympathomimetic drugs :
- High-dose phenylpropanolamine
- Cocaine, amphetamines
- Phencyclidine, epinephrine
- Phenylephrine, and terbutaline
- Combination of MAO inhibitor and ingestion of tyramine-containing foods

History

- Mercury intoxication also can mimic pheochromocytoma, producing both HTN and elevated urine and plasma catecholamines

- If the clinical history suggests the possibility of exposure to any of these drugs, specific testing is warranted

History

- Panic disorder : Panic disorder and ADHD can replicate many of the symptoms of pheochromocytoma because of increased sympathetic activity

- Panic disorder occurs in children, primarily adolescents

History

- Study in which 300 adults were referred for possible pheochromocytoma

- Only one had the disease, but 40 percent met the criteria for panic disorder, compared with 5 percent of control patients with HTN

Indications for biochemical testing

- HTN with features suggestive of secondary HTN, after exclusion of other causes, especially renovascular disease
- HTN in association with other symptoms of sympathetic overactivity, such as episodic headache, sweating, and tachycardia or palpitations
- If the symptoms are not explained by sympathomimetic drugs or panic disorder

Indications for biochemical testing

- Papilledema, focal neurologic deficits, or unrelenting headache, if other causes of intracranial HTN have been excluded

- Incidentally discovered adrenal mass

Initial diagnostic assay

- Measurement of fractionated metanephrines and catecholamines in a 24-hour urine collection, or
- Plasma fractionated metanephrines if an accurate urine collection is not feasible

- When interpreting the results of biochemical testing, it is important to take into account the patient's age

- If one of these tumors is identified, the patient should also be evaluated for an underlying genetic pathogenic variant

Patients with family history

- An asymptomatic person at risk for disease on the basis of family history of pheochromocytoma or PGL, MEN2, or VHL disease :
- should have genetic testing if an affected family member has a known pathogenic variant
- If a disease-causing pathogenic variant is identified, biochemical testing should be performed

Patients with known pathogenic variants

- An asymptomatic person with a genetic disorder :should have periodic screening for development of these and any other associated tumors

- Pathogenic variants in
- SDHA, SDHAF2, SDHB, SDHC, and SDHD (collectively known as SDHx)
- TMEM127, or MAX
- VHL disease (or VHL pathogenic variants) or MEN2 (or RET pathogenic variants)

Patients with known pathogenic variants

- Screening consists of routine biochemical testing and blood pressure measurements and, for some genotypes, periodic imaging

- The preferred case detection method in pediatric patients with one of these pathogenic variants is plasma fractionated metanephrines

Monitoring

Monitoring for pheochromocytoma and paraganglioma in asymptomatic individuals with a predisposing genotype

Genes involved	Blood pressure, symptoms	Biochemical testing (plasma fractionated metanephrines)	MRI (skull base and neck, chest, abdomen, and pelvis)	MRI or CT of the abdomen	PET/CT or PET/MRI
SDHB[1]	Annually	Annually, starting at age 5 years	Every 2 to 3 years, starting at age 6 years		Consider every 5 years
*VHL**[2]	Annually	Annually, starting at age 5 years		If plasma fractionated metanephrines are abnormal, and in women who are planning for pregnancy	
SDHA¶, *SDHAF2*Δ, *SDHC*, or *SDHD*Δ[1]	Annually	Annually, starting at age 10 years	Every 2 to 3 years, starting at age 10 years		Consider every 5 years
TMEM127 and *MAX*	Annually	Annually, starting at age 10 years		If plasma fractionated metanephrines are abnormal, and in women who are planning for pregnancy	
MEN2 A and B due to *RET* variants*[3]	Annually	Annually, starting at age 11 to 16 years depending on RET variant and the risk it confers for pheochromocytoma		If plasma fractionated metanephrines are abnormal, and in women who are planning for pregnancy	
*NF1**[4]	Annually	Not recommended for asymptomatic patients◇			

DIAGNOSTIC TESTING

- Virtually all patients with symptomatic pheochromocytoma have clearly abnormal values for any of these tests
- Normotensive and asymptomatic patients with pheochromocytoma may have normal or mildly abnormal values
- Thus, when a test result is equivocal, a different test should be done
- A variety of drugs can interfere with these tests and should ideally be stopped prior to testing

Medication that increase cathecholamines and metanephrines

- TCA
- Levodopa
- Amphetamines
- Buspirone and most psychoactive agents
- Prochlorprazine
- Resperidone
- Whithdrawal from clonidine and other drugs
- Ethanol
- Drugs containing adrenergic receptor agonist(decongestants)

DIAGNOSTIC TESTING

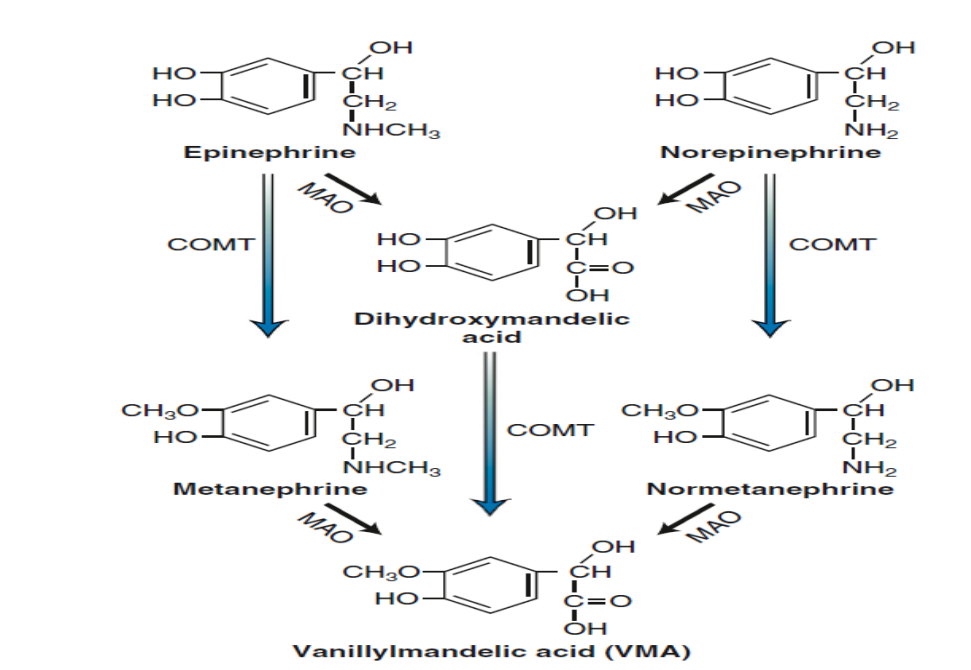
- Measurements of fractionated metanephrines and catecholamines should be performed in reference laboratories that employ HPLC or tandem mass spectrometry technology

Urinary fractionated metanephrines and catecholamines

- For patients who are being evaluated because of symptoms
- 24-hour urinary measurement of fractionated metanephrines (normetanephrine and metanephrine) and catecholamines (norepinephrine, epinephrine, and dopamine) is the most useful test

Urinary fractionated metanephrines and catecholamines

- In general, large tumors produce more metanephrines because the catecholamines are metabolized within the tumor before they are released
- Whereas small tumors are more likely to release free catecholamines



Urinary fractionated metanephrines and catecholamines

- The diagnostic cutoffs used for these tests tend to cause some false-positive testing because they are based on a reference group of healthy normotensive volunteers, rather than individuals with HTN

Urinary fractionated metanephrines and catecholamines

- A 24-hour urine sample is usually collected for these measurements in stable patients
- Urinary creatinine should also be measured
- Shorter collections (overnight) may be more convenient
- but are also more likely to yield false-positive results if they capture acute events associated with sympathetic activity

Plasma fractionated metanephrines

- This test is somewhat more sensitive than 24-hour urinary fractionated metanephrines
- But the increased sensitivity comes at the expense of a suboptimal false-positive rate of 15 percent when performed in a clinical setting

Plasma fractionated metanephrines

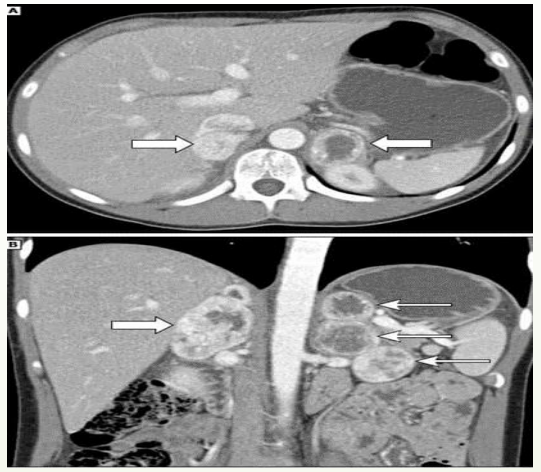
- To minimize false-positive results, blood should be sampled from an intravenous catheter with the patient calm and relaxed
- Patients should be fasting and avoid caffeine and strenuous physical activity for at least 8 to 12 hours before testing

Others

- Measurement of fractionated catecholamines in plasma is not useful (high false-positive)

Imaging

- Abnormal urine or serum test results should be followed by radiologic evaluation to locate the tumor
- 40 to 70 percent of catecholamine secreting tumors in children are in the adrenals
- 30 to 60 percent are extra-adrenal : often located in the superior and inferior para-aortic areas



CT or MRI

- Patients with positive results of biochemical testing :CT or MRI of the abdomen and pelvis
- Either test detects almost all sporadic tumors because most symptomatic neoplasms are 3 cm or larger diameter
- The choice between CT and MRI depends upon the cost and certain other factors

CT or MRI

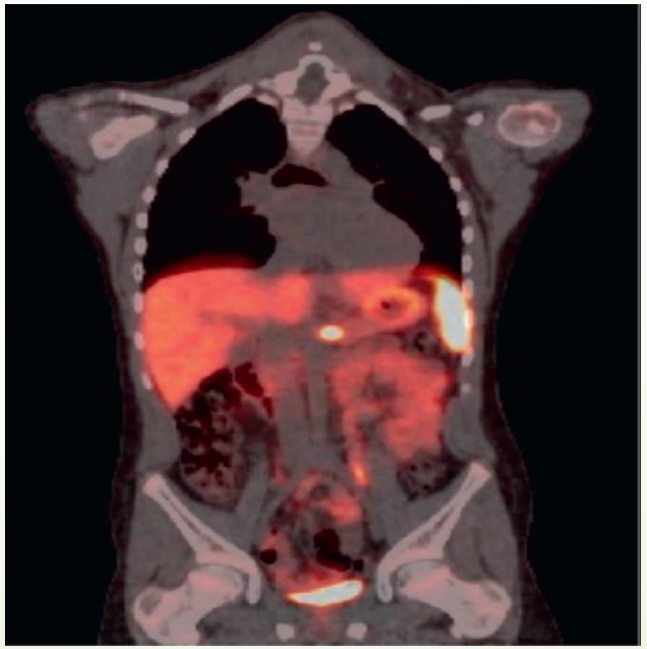
- With CT, there is some exposure to radiation and contrast dye is used
- MRI employs gadolinium and has inferior spatial resolution compared with CT, but avoids exposure to radiation and contrast dye
- In T2-weighted images, pheochromocytomas appear hyperintense and other benign adrenal tumors hypointense, as compared with the liver
- >10 HU

Radionuclide scintigraphy and positron emission tomography

- Scintigraphy with 123I-metaiodobenzylguanidine (MIBG)
- Integrated positron emission tomography (PET) CT or MRI using somatostatin receptor-based diagnostic radionuclides such as gallium Ga-68 DOTATATE, gallium Ga-68 DOTATOC (where available), 18F-fluorodeoxyglucose (FDG), or other compounds

Radionuclide scintigraphy and positron emission tomography

- Candidates for these tests fall into one of two categories:
- Positive biochemical tests, negative CT or MRI of the abdomen and pelvis :
- In this case, total body imaging with Ga-68 DOTATATE PET/CT or MRI is indicated



Radionuclide scintigraphy and positron emission tomography

- Positive biochemical tests, positive CT or MRI :
- In these patients one of these imaging techniques may be performed to evaluate for possible additional tumors

- But expert opinion varies as to whether this is helpful
- Multiple tumors are found in up to 40 percent of children, particularly those with extra-adrenal tumors

Radionuclide scintigraphy and positron emission tomography

- Some clinicians have suggested that PET-based imaging should be performed in all children with catecholamine-secreting tumors, even if a tumor was identified on the CT scan

Radionuclide scintigraphy and positron emission tomography

- However, MIBG scintigraphy has identified apparent extra-adrenal "tumors" that were not confirmed at surgery
- In addition, most clinicians with experience with these patients find that it does not add to the clinical management of patients with solitary adrenal pheochromocytoma identified by CT or MRI

Radionuclide scintigraphy and positron emission tomography

- We suggest total body imaging with Ga-68 DOTATATE PET/CT or MRI for the following groups of patients:

- Patients with biochemical documented disease but negative CT or MRI of the abdomen and pelvis

Radionuclide scintigraphy and positron emission tomography

- Patients with PGL because these patients have a relatively high risk of metastatic disease as well as additional PGL

- Patients who carry a disease-causing SDHx pathogenic variant (SDHA, SDHAF2, SDHB, SDHC, or SDHD); we perform a total body screen scan periodically (every two to five years)

GENETIC TESTING

- Genetic testing should be performed for any pediatric patient diagnosed with pheochromocytoma or PGL
- The type of germline pathogenic variant guides clinical management

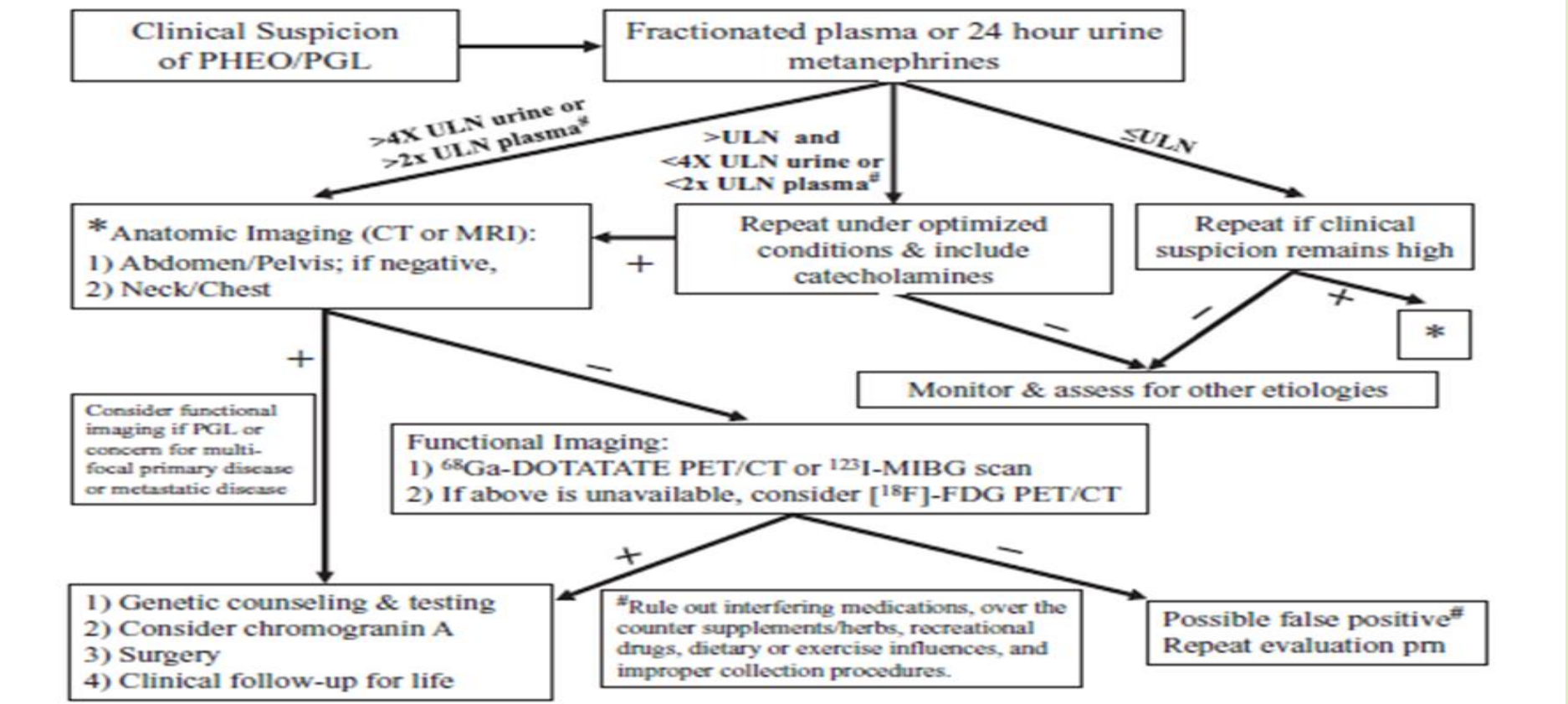
GENETIC TESTING

- The approach to genetic testing depends on the patient's characteristics:
- Pheochromocytoma or paraganglioma and known syndrome : VHL disease, MEN2, NF1, or familial paraganglioma should have targeted pathogenic variant testing for the causal genes

GENETIC TESTING

- Sporadic pheochromocytoma or paraganglioma : Patients with apparently sporadic disease also should undergo genetic testing.
- The field of genetic testing is rapidly evolving, and at many clinical laboratories, sequential genetic testing is no longer done, as it is less expensive to utilize next-generation sequencing technology for all clinically available pathogenic variants as a package

Diagnostic approach



Treatment

- Once a pheochromocytoma is diagnosed, the patient should undergo surgery after appropriate medical preparation
- Preoperative resolution of symptoms and normalization of BP are predictors of an uncomplicated outcome

Medical preparation for surgery

- In patients with catecholamine-secreting tumors, surgery can provoke hypertensive crises and malignant arrhythmias
- Patients are also at risk for postoperative hypotension due to chronic vasoconstriction and volume contraction

Medical preparation for surgery

- Antihypertensive treatment (typically with adrenergic blockade) is recommended for all patients, regardless of whether they have hypertension preoperatively

Medical preparation for surgery

- Alpha-adrenergic blockade method : Although no method of preparation for surgery in children with pheochromocytomas is universally accepted
- Common approach is to initiate alpha-adrenergic blockade, followed by beta-adrenergic blockade if needed:

Medical preparation for surgery

- Alpha-adrenergic blockade : We generally use alpha adrenergic blockade with phenoxybenzamine unless contraindicated (cardiopulmonary concerns)
- The starting dose of phenoxybenzamine in children is 0.25 to 1.0 mg/kg per day or 10 mg once daily
- The dose is increased every few days until the patient's symptoms and BP are controlled

Medical preparation for surgery

- Due to the high cost of phenoxybenzamine, some clinicians may choose to a selective alpha-1 antagonist (doxazosin, terazosin, or prazosin)

- Typically, alpha-adrenergic blockade is started 7 to 14 days before surgery
- Treatment targets include resolution of paroxysmal symptoms and a systolic BP that is in the lower end of the normal range for age

Medical preparation for surgery

- Volume expansion : On the second or third day of alpha-adrenergic blockade, patients are encouraged to start a diet high in sodium content because of the catecholamine-induced volume contraction and the orthostasis associated with alpha-adrenergic blockade

- This causes intravascular volume expansion, which may be contraindicated in patients with heart failure or kidney function impairment

Medical preparation for surgery

- Beta-adrenergic blockade : After adequate alpha-adrenergic blockade has been achieved, which typically occurs two to three days preoperatively, beta adrenergic blockade is initiated if needed to control tachycardia

- The beta adrenergic blocker should never be started first because blockade of vasodilatory peripheral beta-adrenergic receptors with unopposed alpha-adrenergic receptor stimulation can lead to a further elevation in BP

- The clinician should exercise caution if the patient is asthmatic or has heart failure

Medical preparation for surgery

- Chronic catecholamine excess can produce a cardiomyopathy that may become evident with the initiation of beta adrenergic blockade, resulting in acute pulmonary edema
- Therefore, when the beta-adrenergic blocker is administered, it should be used cautiously and at low dose
- The dose is then increased as necessary to control the tachycardia
- In most cases, the patient is ready for surgery in 10 to 14 days after starting the alpha-adrenergic blockade

Other methods

- Although perioperative alpha blockade is widely recommended, a second regimen that has been utilized in adults at the Cleveland Clinic and in France involves the administration of a calcium channel blocker for blood pressure control

- In a review of 113 adult patients who underwent removal of pheochromocytomas, fewer perioperative complications were observed in those not given alpha-adrenergic antagonists

Other methods(metyrosine)

- A third approach is to administer metyrosine (alpha-methyl-para-tyrosine), which inhibits catecholamine synthesis by blocking the enzyme tyrosine hydroxylase
- Metyrosine should be used with caution and only when other agents have been ineffective or if significant tumor manipulation is anticipated
- Although some centers have used this agent routinely, most clinicians reserve metyrosine primarily for patients who cannot be treated with the combined alpha- and beta-adrenergic blockade protocol because of intolerance or cardiopulmonary concerns

Other methods(metyrosine)

- Side effects of metyrosine can include orthostatic hypotension, diarrhea, sedation extra-pyramidal symptoms and crystalluria
- The use of metyrosine is also limited by its high cost

Drug Class	Drug	Mechanism of Action	Initial Pediatric Dose
α-adrenergic receptor blockers	Doxazosin	α_1-antagonist	0.5–1 mg daily
	Phenoxybenzamine	α_1- and α_2-antagonist	0.2–0.25 mg/kg/d divided BID (max 10 mg BID)
	Prazosin	α_1-antagonist	0.05–0.1 mg/kg/d divided TID (max 1 mg TID)
β-adrenergic receptor blockers	Atenolol	β_1- antagonist	0.5–1 mg/kg/d daily or BID (max 50 mg daily)
	Metoprolol	β_1- antagonist	1-2 mg/kg/d divided BID (max 50 mg BID)
	Propranolol	β_1- and β_2-antagonist	1–2 mg/kg/d divided BID or TID (max 80 mg daily)
Calcium channel blockers	Amlodipine	Calcium channel blocker	0.1 mg/kg/d (<6 years); 2.5–5 mg daily (age ≥6 years)
	Nifedipine (sustained release)	Calcium channel blocker	0.25–0.5 mg/kg/d daily or BID (max 60 mg total daily dose)
Inhibitors of catecholamine synthesis	Metyrosine	Tyrosine hydroxylase inhibitor	125–250 mg QID

Surgery

- Surgical removal of pheochromocytomas or PGL in children usually results in the restoration of normal blood pressure ,unless a remaining tumor is present
- The late return of hypertension frequently signals recurrent disease
- With removal of all tumor tissue, catecholamine secretion and the BP should fall to normal levels within one week
- Laparoscopic surgery may be performed in patients with unilateral or bilateral adrenal pheochromocytoma

Surgery

- Paragangliomas usually require an open surgical approach
- When bilateral adrenal pheochromocytomas are present, as sometimes occurs in patients with VHL disease or MEN2:
- bilateral total laparoscopic adrenalectomy should be considered in patients with MEN2
- whereas bilateral cortical sparing adrenalectomy can be considered in non-MEN2 patients

Surgery

- The intent of cortical-sparing adrenalectomy is to leave enough cortex intact to avoid permanent adrenal insufficiency
- However, it is important for clinicians and the child's family to understand that in the setting of MEN2, the medullary involvement is diffuse and that it is impossible to preserve viable cortex without also preserving adrenal medulla

Surgery

- In the setting of MEN2 treated with cortical-sparing surgery, diseased medulla is purposely being left behind and over time it may grow large enough to necessitate a second operation

- Thus, the risk of cortical-sparing adrenalectomy in patients with MEN2 is recurrent pheochromocytoma, which occurred in 3 of 14 patients (21 percent) in one series

Surgery

- Primary adrenal insufficiency occurred in all patients treated with total adrenalectomy but only in 23.5 percent of patients treated with attempted cortical-sparing adrenalectomy

- Familial pheochromocytoma patients with unilateral disease should be treated with unilateral adrenalectomy, even though they are at risk for metachronous disease in the contralateral gland

Surgery

- Sodium nitroprusside is an ideal vasodilator for intraoperative management of hypertensive episodes because of its rapid onset of action and short duration of effect.
- Intravenous infusion at 0.5 to 5 μg/kg of body weight per minute
- adjusted every few minutes for target blood pressure

Malignant disease

- Surgical removal of the tumor is the primary therapy for malignant pheochromocytoma and can be curative

- Patients with metastatic disease should be treated by surgical debulking and chronic medical therapy with alpha adrenergic and, if needed, beta-adrenergic blockade to control symptoms

Monitoring

- Long-term monitoring is indicated in all patients, even those who are apparently cured
- All patients should be evaluated annually, using biochemical testing (plasma or 24-hour urine fractionated metanephrines)

- Those at increased risk for recurrent disease (eg, those with familial, large, extra-adrenal, or bilateral disease) should be reevaluated annually

Monitoring

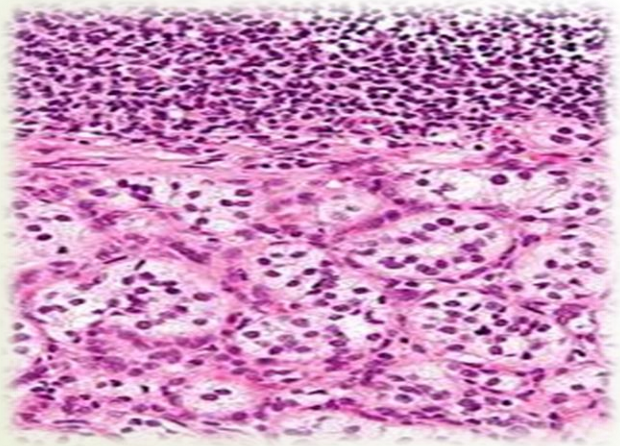
- Surveillance with MRI is indicated in the following clinician scenarios:
- Patients who had a nonfunctioning paraganglioma or pheochromocytoma resected because they lack a tumor marker that can be measured in the blood or urine

Monitoring

- Patients at high risk for developing nonfunctioning (typically in the skull base, neck, and upper mediastinum) paragangliomas (eg, SDHx or VHL pathogenic variant carriers)
- Routine surveillance imaging for pheochromocytoma or paraganglioma is not indicated in patients with MEN2 or neurofibromatosis type 1 (NF1)
- Patients with any SDHx pathogenic variant should have periodic MRI of the abdomen, pelvis, skull base, and neck (every two to three years)

Case

- درمان با پرازوسین 14 روز قبل از جراحی و سپس ایندرال
- فشار خون طبیعی تحت درمان
- تحت جراحی قرار گرفت
- بیوپسی:پاراگانگلیوما



Lab data F/UP

- Urine: Epi:6.3 < 20
- Nepi :16 <90
- Metanephrine:90 <350
- Normetanephrine:274 <600

Lab data F/UP

- Plasma Metanephrine:47 up to 100
- Plasma Normetanephrine:144 up to 220

Plan

- Genetic study
- Screening of at risk families
- Ophthalmologic consult
- Lifelong monitoring

References

- Williams Textbook of Endocrinology,15th ed
- Uptodate 2024
- Sperling Pediatric Endocrinology,5th ed


Thanks for your attention