



"The Scream" by Edvard Munch

"NO TUMOR, YET SYMPTOMS"

PHEOPARA ALLIANCE WEBINAR

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DISCLOSURES

No financial disclosures related to this talk

OBJECTIVES

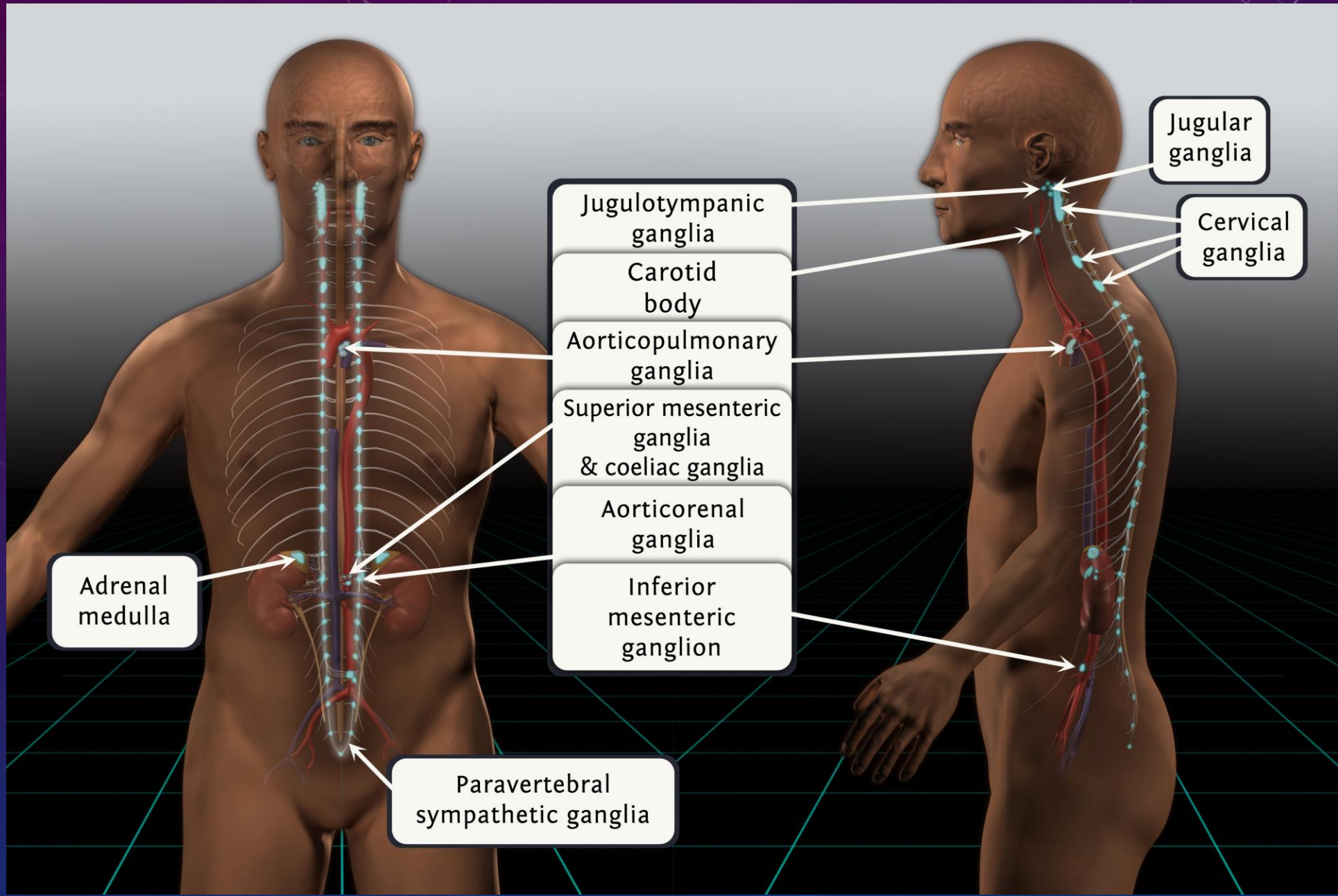
- 1. Consider the evaluation of persistent symptoms of pheochromocytoma, yet no tumor.
- 2. Treatment options?

CASE 1

- 60 year-old male had a head and neck PGL with an unknown pathogenic variant
- Operated and PGL was removed
- Afterwards:
 - Swings in blood pressures
 - Catecholamines and imaging negative!!
- What's going on?

SIGNS AND SYMPTOMS OF PHEOCHROMOCYTOMA

- Nervousness/anxiety,
- Flushing,
- Profuse sweating,
- Palpitations,
- Headache
- Less common manifestations may include chest pain, nausea, vomiting, dizziness, paleness.



PLASMA AND URINARY METANEPHRINES

Table 5. Comparison of Diagnostic Performance of Plasma Free Versus Urinary Fractionated Metanephrines from 5 Available Studies

First Author, Year (Ref.)	Sensitivity		Specificity	
	Plasma	Urine	Plasma	Urine
Lenders, 2002 (39)	98.6% (211/214)	97.1% (102/105)	89.3% (575/644)	68.6% (310/452)
Unger, 2006 (42)	95.8% (23/24)	93.3% (14/15)	79.4% (54/68)	75.0% (39/52)
Hickman, 2009 (46) ^a	100.0% (14/14)	85.7% (12/14)	97.6% (40/41)	95.1% (39/41)
Grouzmann, 2010 (48)	95.7% (44/46)	95.0% (38/40)	89.5% (102/114)	86.4% (121/140)
Unger, 2012 (53)	89.5% (17/19)	92.9% (13/14)	90.0% (54/60)	77.6% (38/49)

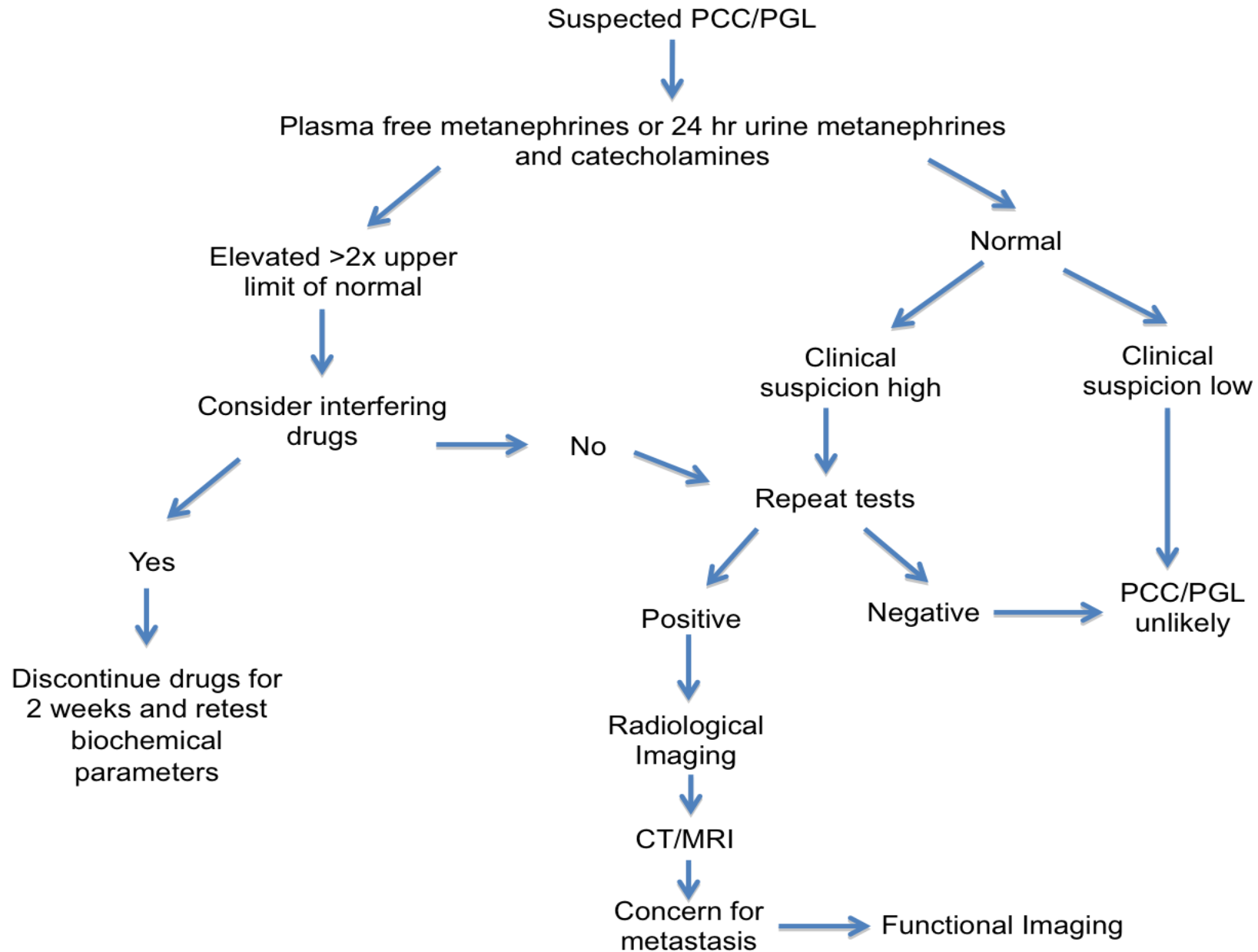
^a Data restricted to that available from Table 4 of those studies where all measurements were made.

Beware of Medications Causing False Positive Results!!

Table 2

Medications often responsible for false positive results in PCC/PGL diagnosis

Medication	High Metabolite Level (False Positive Result for PCC/PGL diagnoses)
α -Blockers	Norepinephrine, normetanephrine
Caffeine	Norepinephrine, epinephrine
Cocaine	Norepinephrine, epinephrine
Levodopa	Norepinephrine
MAO inhibitors	Normetanephrine, metanephrine
Sympathomimetics (ephedrine, albuterol, amphetamines)	Norepinephrine, epinephrine, Normetanephrine, metanephrine
Tricyclic antidepressants	Norepinephrine, normetanephrine



STILL PERSISTENT SIGNS AND SYMPTOMS!

- Recurrence?
 - Pathogenic variants- *SDHB, HIF2-alpha, ATRX, FH, MAX, MAML3*
 - However, our patient doesn't have any of these pathogenic variants!
 - Note- if metanephrines are negative, and there is **NO tumor** on imaging, **symptoms are less likely related** to pheochromocytoma as they continuously release hormones where stable breakdown products can be measured.



ANOTHER
DIAGNOSIS?

ANOTHER DIAGNOSIS?

- Differential diagnosis:
 - Kidney related high blood pressure?
 - If *SDHx* pathogenic variant, some patients can get kidney cancer, so blood pressures can increase- but NO erratic symptoms like pheochromocytoma.



MASTOCYTOSIS

- Mastocytosis is a rare disorder characterized by abnormal accumulation and activation of immune cells in the skin, bone marrow and internal organs.
- Skin lesions?
- Flushing?
- Itching?
- Diarrhea?



CARCINOID?

Due to hormones
that cause:

- Flushing,
- Fast heartbeat,
- Difficulty breathing
- Diarrhea

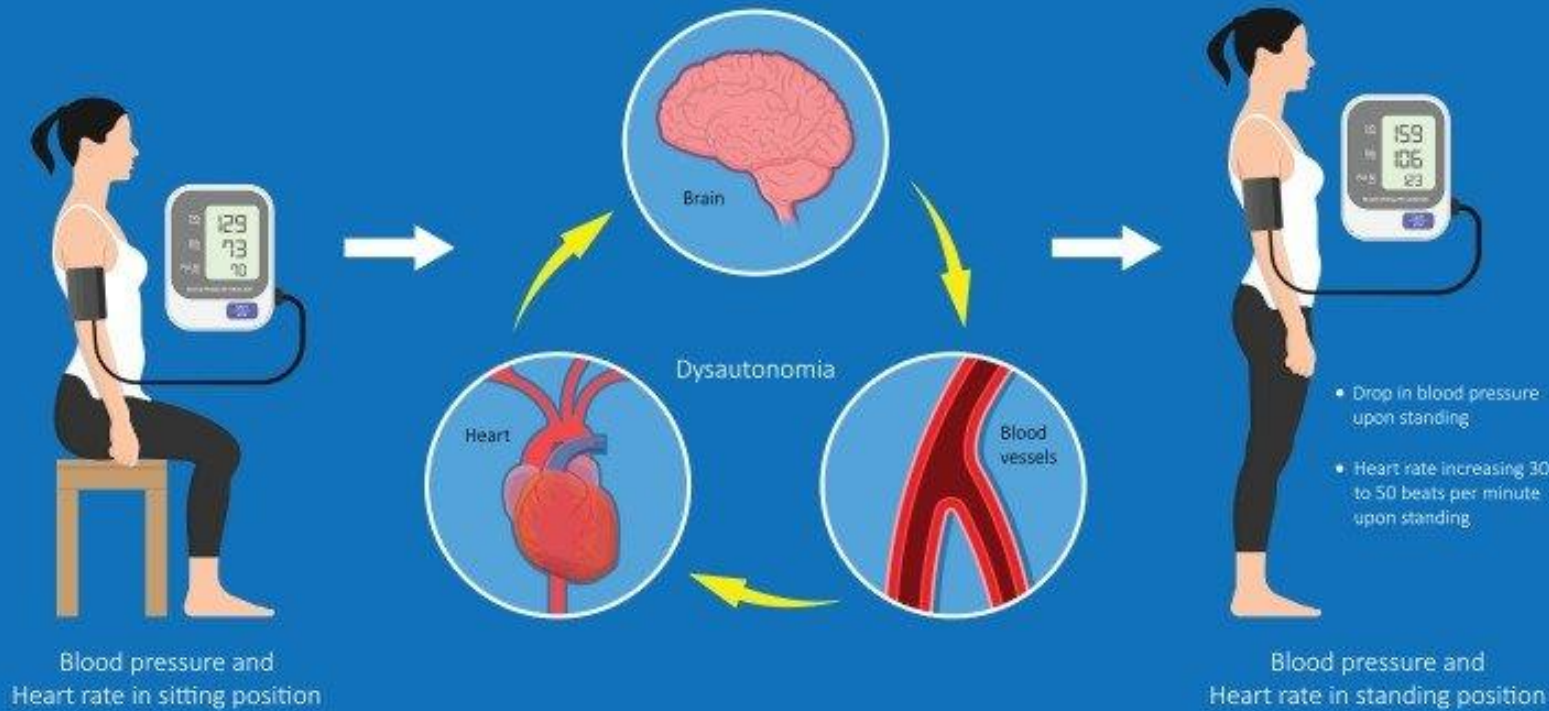


THYROID?

- Hyperthyroidism:
 - Fast heartbeat
 - Nervousness
 - Tremor
 - Sweating



Postural Orthostatic Tachycardia Syndrome (POTS)



Symptoms of POTS

- Dizziness or light-headedness
- Shaking and sweating
- Weakness and fatigue
- Shortness of breath
- Chest pain
- Fainting
- Heart palpitations
- Headaches
- Poor sleep

Postural: Related to the position of your body.

Orthostatic: Related to standing upright.

Tachycardia: A heart rate over 100 beats per minute.

Syndrome: A group of symptoms that happen together.

Not able to coordinate the balancing act of blood vessel constriction (squeezing) and heart rate response.

POTS

- Higher risk of developing POTS after experiencing the following stressors:
 - Significant illnesses, such as viral illnesses like mononucleosis or serious infections.
 - Pregnancy.
 - Physical trauma, such as a head injury.
 - Surgery.

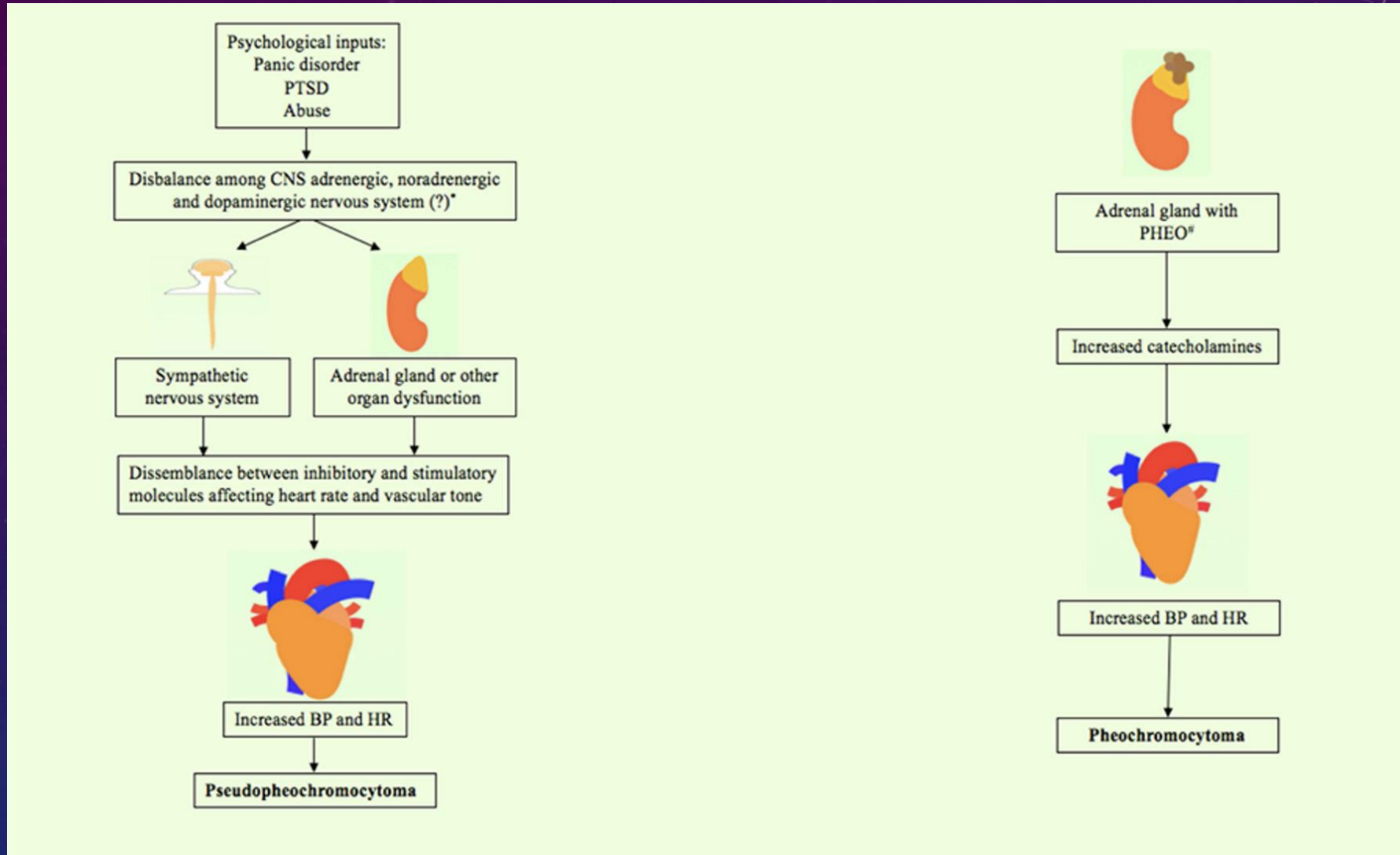
The background is a dark blue gradient with a subtle pattern of white stars and technical diagrams. On the right side, there are several circular diagrams resembling gauges or dials. One large gauge has a scale from 0 to 210 in increments of 10. Other smaller gauges and dashed circular paths with arrows are scattered across the background. The text is centered in the middle of the image.

PSEUDOPHEOCHROMOCYTOMA?
(PSEUDOPHEO)

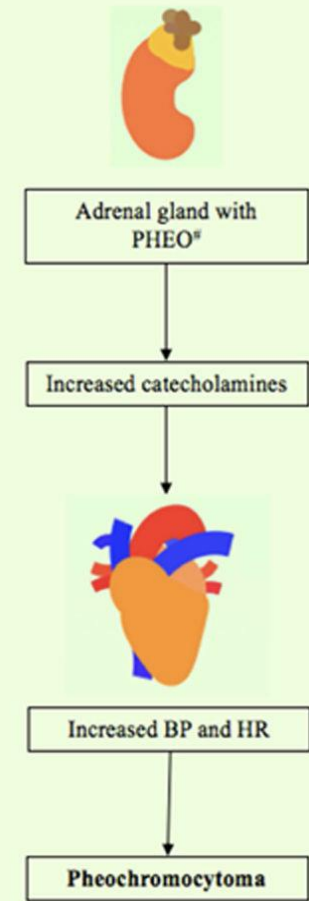
WHAT IS PSEUDOPHEO?

- Clinical presentations of PSEUDOPHEO are similar to that of PHEO:
- Recurrent peaks in blood pressure, however, showing no anatomical and biochemical abnormality
 - altered function of the autonomic nervous system or abnormal disposition of catecholamines released from neurons within the brain.
- Absence of an adrenal tumor on imaging studies are useful to delineate PSEUDOPHEO from a typical PHEO.

Pseudopheochromocytoma



Pheochromocytoma



*Stimulation of a neural limb causes an increased norepinephrine release

*Stimulation of a adrenal limb causes an increased epinephrine release causing increased heart rate

PSEUDOPHEO

- Unknown etiology,
- Unidentified pathophysiological mechanisms,
- Often amplified cardiovascular responses utilizing antihypertensive medications.
- Diagnosis of exclusion

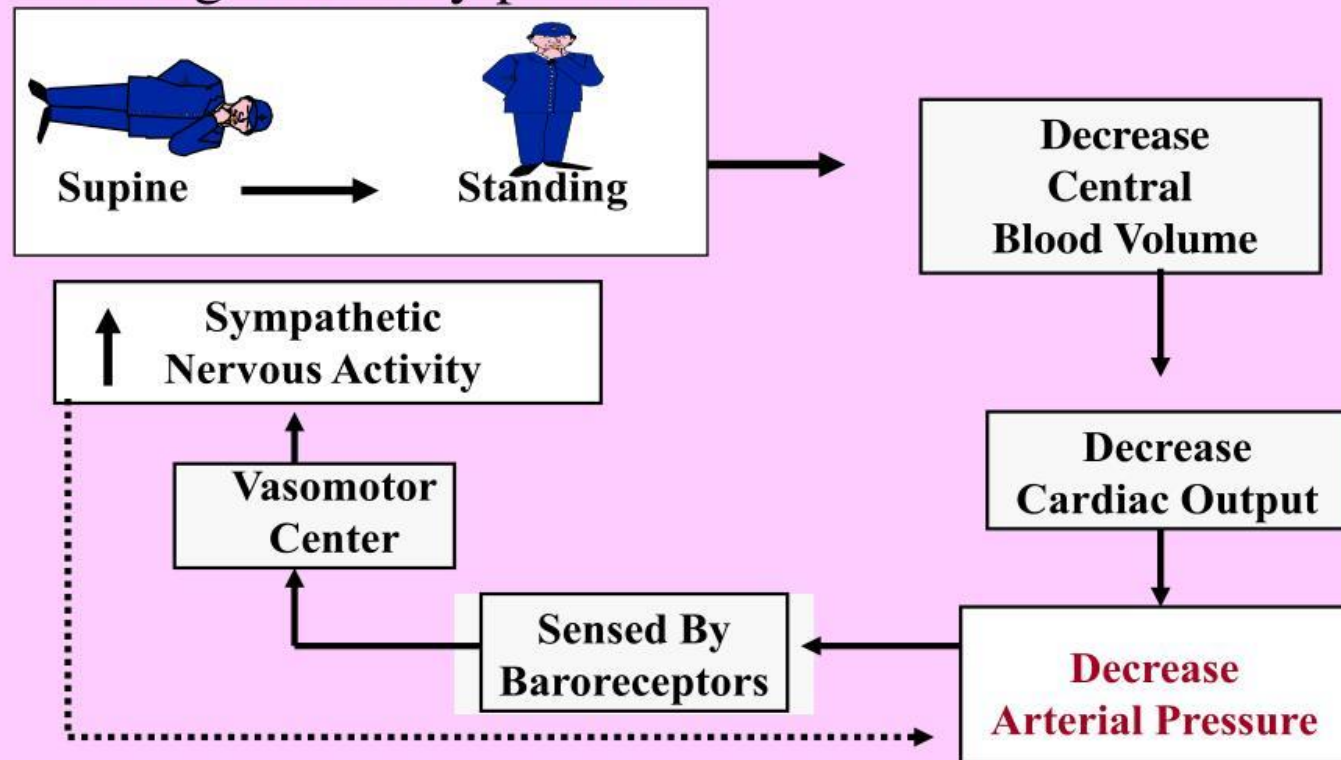
PseudoPHEO- Remember it's a diagnosis of exclusion!	Other differentials
PseudoPHEO _ No injury or neck surgery	Baroreceptor failure is due to: accidental injury, neck surgery, or irradiation and is associated with both hypertension and hypotension

CASE 1

- 60 year-old male had a head and neck PGL with *SDHD* pathogenic variant
- **Operated on neck PGL**
- No tumor
- Swings in blood pressures
- Catecholamines and imaging negative!!
- What's going on?

Functions of the Baroreceptors

- Maintains relatively constant pressure despite changes in body posture.



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PseudoPHEO - + Headaches	Panic Disorder- blood pressure elevation in panic disorder is not as high as it is in pseudoPHEO

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PseudoPHEO – No traumatic event	Post traumatic stress disorder- Traumatic event causes changes in catecholamines causing symptoms

CASE 2

- 37 year-old male presents to emergency room with hypertensive urgency
- Blood pressures: 190/100 mmHg
- Heart rate 105 beats per minute
- He had a history of pheochromocytoma surgically removed 1 year ago. Biochemical work-up from 6 months ago was normal.

CASE 2

- He has symptoms of headaches, palpitations often and on.
 - Occasional spikes in blood pressures 2-3 times a month
 - Other history: in the last year has been having more allergies
- No known genetic mutations
- Repeat biochemical evaluation showed normal metanephrines
- CT scan showed thickness in the left adrenal gland

CASE 2

- Thyroid disease ruled out
- Mastocytosis ruled out
- Carcinoid ruled out
- Vasculitis ruled out
- Further history: recent anxiety due to job related issues. Worried about next meal, had been drinking more caffeinated beverages to stay up and finish work.



MANAGEMENT

- Depends on the underlying diagnosis
- Possible management of symptoms with blood pressure medications
 - Different classes of medications tend to be helpful:
 - Calcium channel blockers
 - β -blockers
 - α -blockers

PREVENTIVE MEASURES

A well tolerated approach would be a combination of α -adrenoceptor blocker and β -adrenoceptor blockers



In specific cases:

Antidepressants in consultation with a psychologist/psychiatrist helpful in certain cases of increased anxiety and depression

Address repressed emotions regarding their disease state

CONCLUSIONS

- If the work-up for recurrence is negative, these symptoms are not imaginary as they **can** exist.
- **If metanephrines are negative, and there is NO tumor on imaging, symptoms are less likely related to pheochromocytoma** as they continuously release hormones where stable breakdown products can be measured.



CONCLUSIONS

- If no tumor is found a differential diagnosis should be considered.
- Symptomatic treatment with α , β , or calcium channel blockers can be helpful in selective patients.
- As these symptoms can be challenging, continue to follow with healthcare team.

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THANK YOU!



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