35 Year Old female with bilateral neck mass

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HPI

- 35 year old F with PMH of HTN, asthma.
- Was in her usual state of health until 2 years ago
- c/o intermittent palpitation + Wt loss à blood drawn à abnormal TFT
- Abnormal exam à US thyroid showed large bilateral neck mass not associated with her thyroid
- No h/o voice change, neck pain, difficulty swallowing, increase in sweating, headache or change in her periods.

PMH:

- Mild intermittent asthma
- HTN
- Anxiety

Family History:

- No FH of thyroid cancer
- No FH of neck tumor

Surgical history:

- None

Social history

- Never smoke, no alcohol, no illicit drugs.

Home medications

- Albuterol PRN
- Diltiazem 240 mg po daily
- Clonazepam PRN (anxiety)

ROS

Constitutional: Wt loss (40 pounds over 2 years)

HENT: No blurred vision, no double vision, no sore throat, no headache.

Neck: + neck mass, no neck pain

Cardio/pulm: No CP, + intermittent palpitation, no orthopnea or PND

GI: No N/V/D, no constipation, no melena or hematochezia

GU: Negative, normal menses

Skin/MSK: negative, no rash

Neuro negative

On examination

Vitals: BP 134/94, Pulse 88, no fever, RR 14, BMI 21

General: awake alert, comfortable

HEENT: normocephalic non traumatic, no pallor, no jaundice. No double vision, no increase insertion, no exophthalmos

Neck: supple, no thyromegaly, small bilateral pulsatile, non tender masses in the upper part of the neck.

CVS/Pulm: clear equal air entry no added sounds, regular pulse, S1 + S2, no murmur.

Abd: soft lax, no organomegaly, no tenderness, audible bowel sounds.

Skin: normal, not diaphoretic

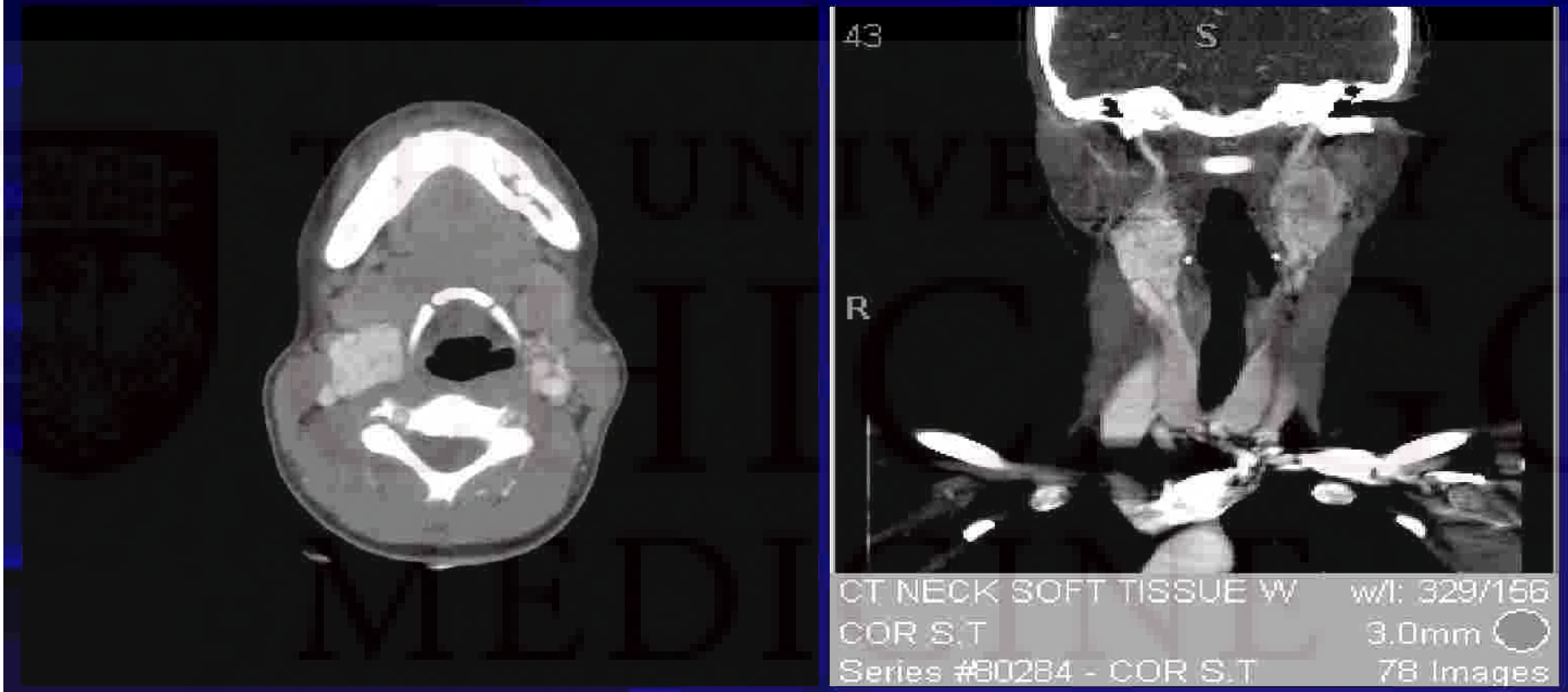
Lymphatic: No cervical, axillary or inguinal Lymphadenopathy

Neuro: alert, no tremor, CN intact, DTR normal

Psych: normal mood, and affect

Radiology ((outside facility))

CT scan neck



a) Enhancing masses at the level of the carotid bifurcations.
b) The right mass measures 3.2 x 2.6 x 5.3 cm, Lt mass 2.7 x 1.7 x 4.4 cm

Differential Diagnosis

1. **Carotid artery**
   - Aneurysm
   - Pseudo aneurysm
   - Dissection
2. **Jugular Vein**
   - Thrombosis
   - Thrombophlebitis
3. **Inflammatory**
   - Abscess
4. **Lymph nodes**
   - Metastaic LN
   - Lymphoma
5. **CN ((X, XI, XII, sympathetic chain))**
   - Paraganglioma
   - Neuroblastoma

General labs

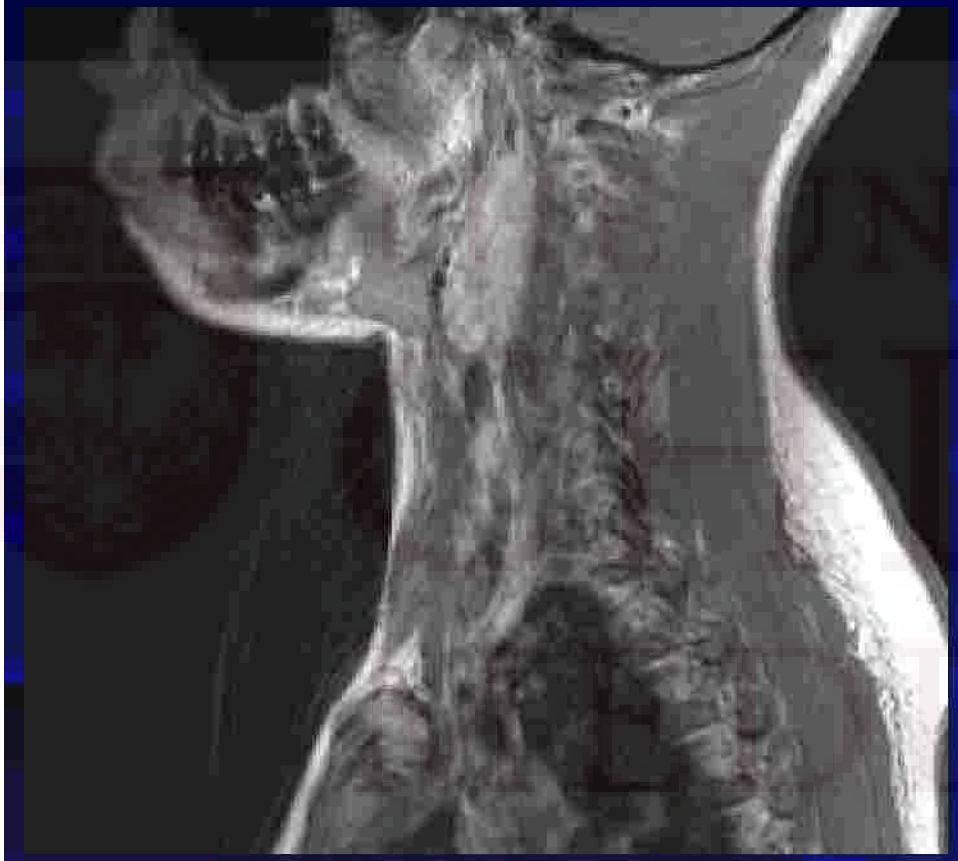
Test/date	11/2013
Na/K	138/3.7
BUN/Cr	6/0.8
eGFR	84
ALP	83
ALT/AST	9/12
Hb	11.6
WBC	7.6
Plt	322

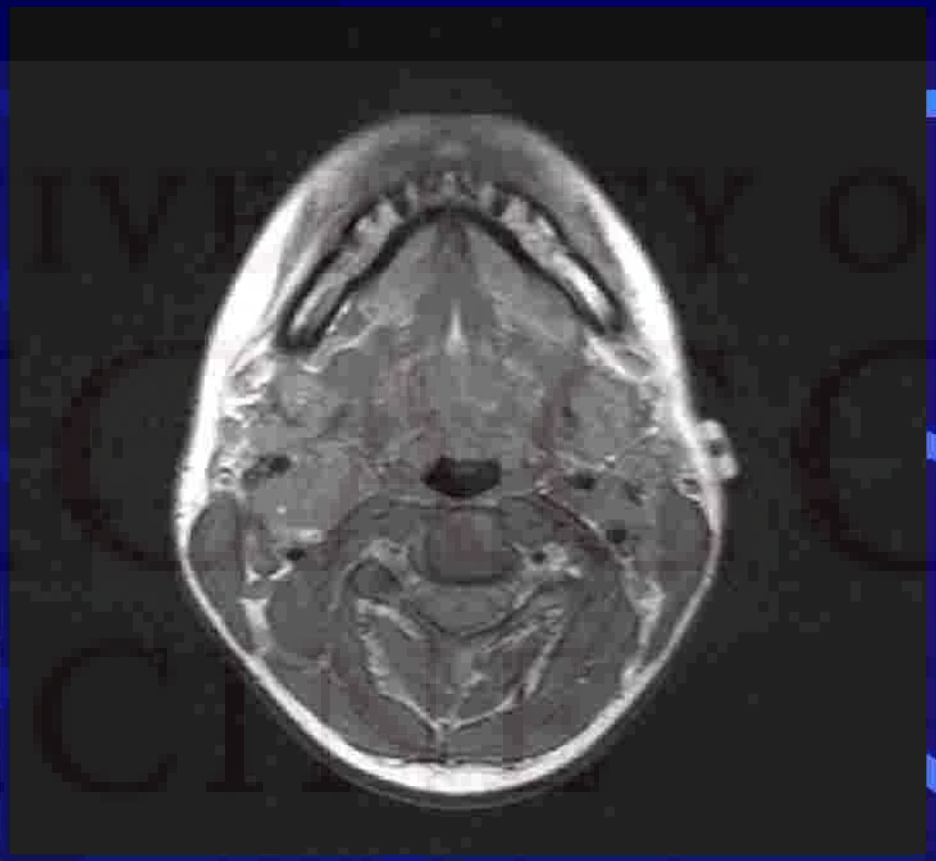
Endocrine work up

Test/date	2/12	6/12	9/12	12/12	2/13	5/13	8/13	11/13
TSH (0.4 – 4.5)	6.59	6.27	4.157	0.41	0.16	3.46	6.32	2.45
FT4 (0.8 – 1.8)		0.85	1.06		1.06	0.89	0.74	1.06
T3 (20 – 195)						106		97
FT3 (0.6 – 1.8)	1.27	2.18	1.81					
TPO Ab					20			
Tg Ab					640			
TSI					<1.0			

Test/date	10/2012	2/2013	11/2013
Catecholamines timed urine			
NE (ref: 15 - 80 mcg/24hrs)		*NE 94*	
E (ref: 0 - 20 mcg/24hrs)		E 9.0	
Dopamine (ref: 65 – 400 mcg/24hrs)		D 320	
Plasma Metanephrines			
Normetanephrines (< 0.9)		*NM 1.5*	NM 0.58
Metanephrines (< 0.5)		M 0.3	M <0.2
VMA urine (ref < 8.0)	3.0	5.2	

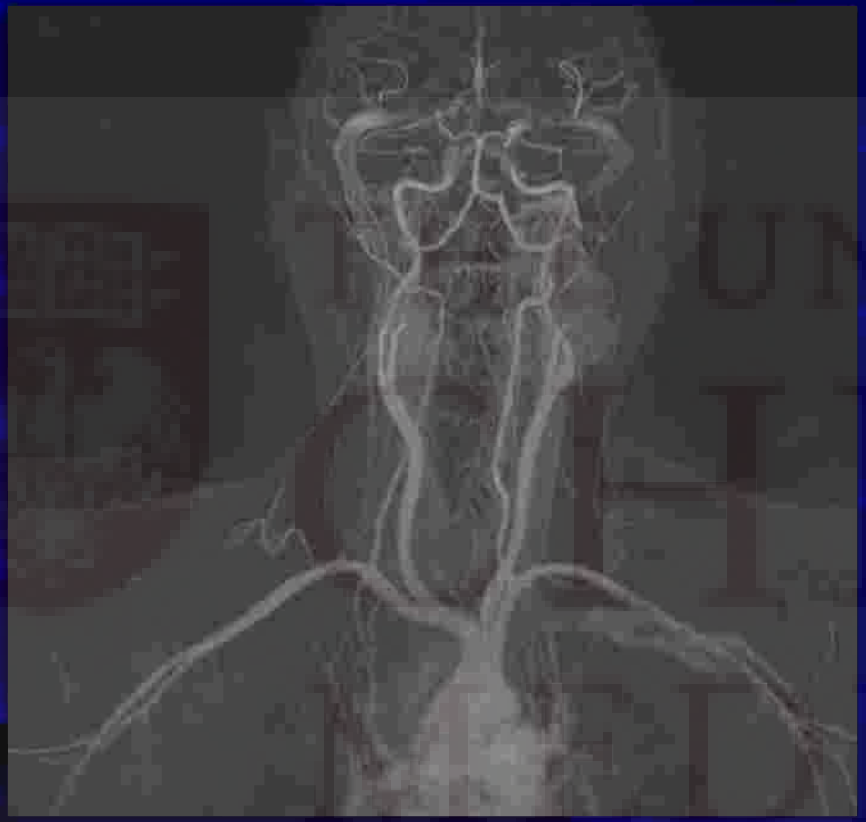
MRI neck





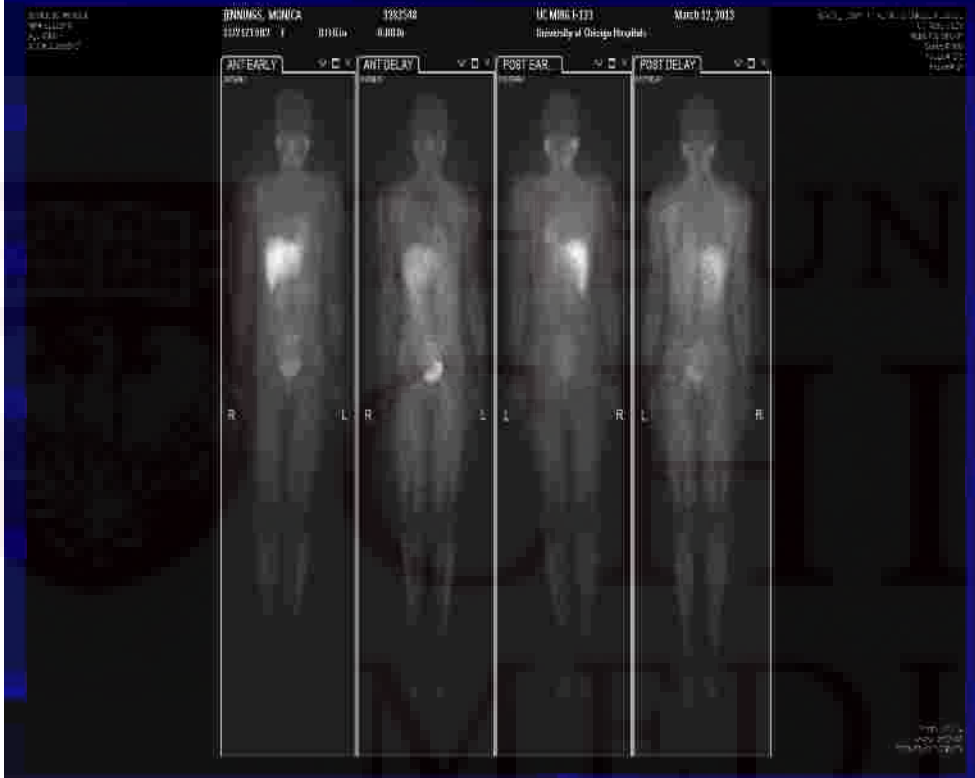
T1 MRI: Enhancing masses, the right mass measures 3.2 x 2.6 x 5.3 cm, Lt mass 2.7 x 1.7 x 4.4 cm.

MRA



a) Bilateral internal and external arteries are splayed by bilateral tumors.
b) Despite encasement by the tumors, both internal and external carotid arteries demonstrate normal caliber without convincing irregularity or narrowing

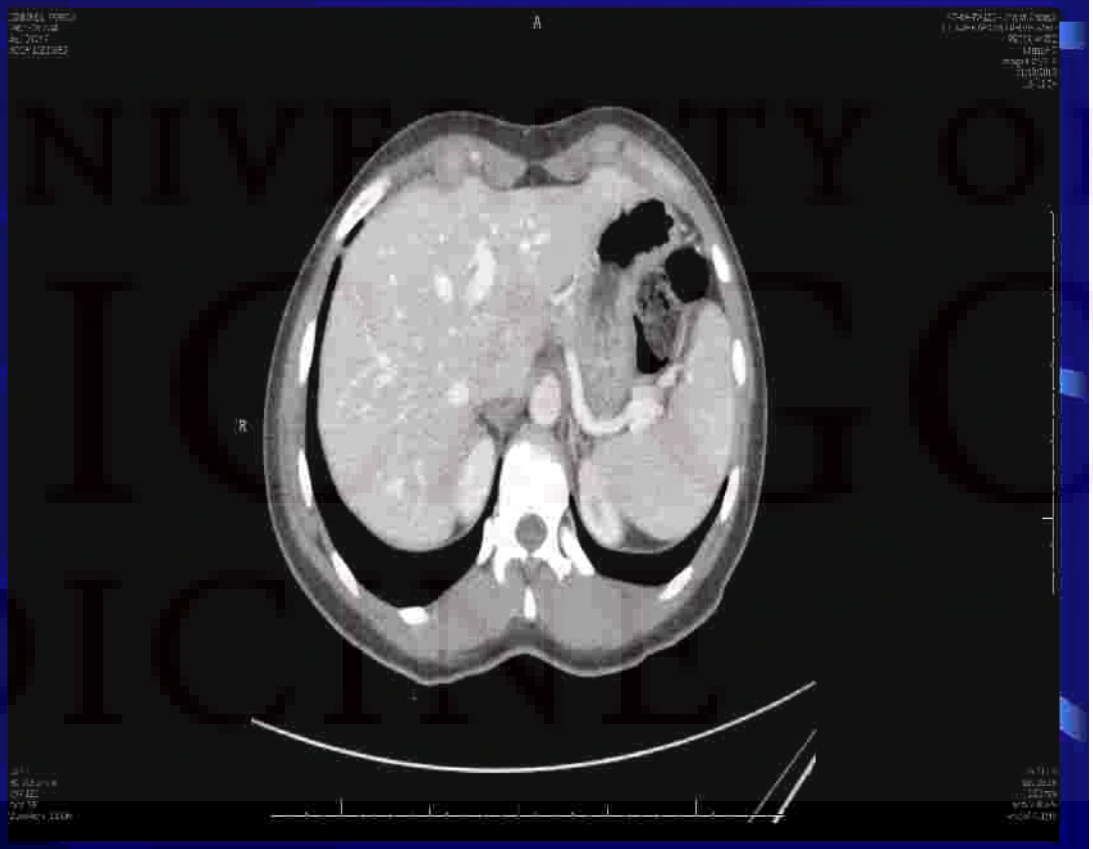
MIBG



a) Normal physiologic radiotracer distribution is seen in e salivary glands, myocardium, liver, bowel and bladder
b) Asymmetrically increased activity in the right suprarenal region raises the question of a pheochromocytoma

MRI/CT abdomen & pelvis

- **MRI adrenal glands**
  - No significant abnormality noted, no focal nodularity or mass lesion is identified. No evident lesion to correlate with the abnormal MIBG scan.
- **CT abdomen**
  - No evidence for adrenal mass or peri-aortic paraganglioma



Underwent surgical resection of both masses

Pathology report:

Paraganglioma (5.1 cm) in Rt carotid bifurcation

Paraganglioma (3.5 cm) in Lt carotid bifurcation

Genetic testing

Deleterious mutation was detected in the ***SDHD*** gene

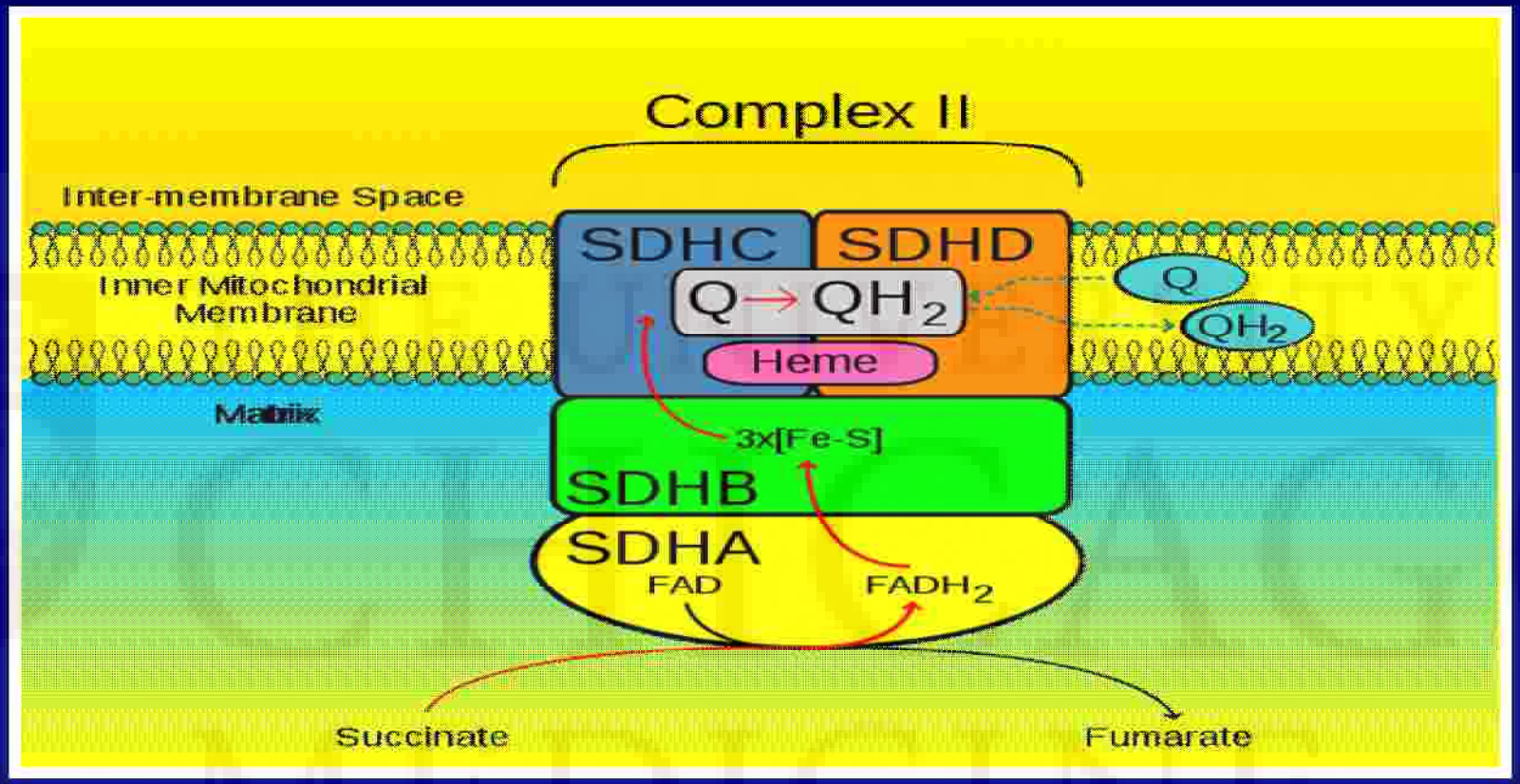
Clinical Qs

- What is the prevalence of pheochromocytomas in patient with SDHD-associated head-and-neck paragangliomas?
- How common is SDHD-associated head-and-neck paragangliomas (HNP) with negative FH?

Few lines on PG

- Is a rare neuroendocrine tumor
- Accounts for 0.012% of all human tumors and 0.6 % of a l H&N neoplasm.
- 75% of PG are sporadic and 25% are hereditary
- H&N PG commonly originate from paraganglion cells in carotid body, vagal nerve, middle ear, and Jugular foramen (Glomus tumor)
- 80% of these are either carotid body or Jugular area.

SDH Complex II



- **SDH complex** is located on the **inner membrane of the mitochondria** and participates in both the ***Citric Acid Cycle and electron transfer chain***
- **SDHA** converts **succinate to fumarate**. This reaction also converts FAD to $FADH_2$.
- Electrons from the $FADH_2$ are transferred to the SDHB
- **Hereditary paraganglioma syndrome is due to mutations in one of three genes: SDHB, SDHC, SDHD (succinate dehydrogenase subunit B, C, or D)**

Few words on SDH mutations

- SDH mutations are inherited in a dominant manner.
- This means that there is a **50% chance** that the offspring of an individual with a SDH mutation will inherit the disease. Men and women are equally likely to inherit it.
- **The exception** to this inheritance pattern is **SDHD** gene mutations, which are still inherited in a dominant manner, but individuals only develop tumors ***if the gene mutation is inherited from their father***.

Pheochromocytomas and extra-adrenal Paragangliomas detected in screening patients with SDHD head-and-neck Paragangliomas.

B Havekes[1], A A van der Klaauw[1], M M Weiss[2], J C Jansen[3], A G L van der Mey[3], A H J T Vriends[2], B A Bonsing[4], J A Romijn[1] and E P M Corssmit[1]

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Endocrine-Related Cancer (2009) 16 527–536

- Data reviewed of all consecutive HNP patients who visited the outpatient clinic at the Department of Endocrinology since 1988
- 154 pts with HNPG
- **93 patients** with **SDHD** associated HNP included in the study.
- Screening consisted of measurement of 24 h urinary excretion of catecholamines and/or their metabolites.
- In patients, in whom urinary excretion was above the reference limit, imaging studies with **MIBG** and **MRI** and/or **CT** were performed.
- Median follow-up was **4.5 years** (range 0.5–19.5 years)

Endocrine-Related Cancer (2009) 16 527–536

No.	Sex, age (years)[a]	HTN	Start screening	Dx	FH of PG
1	M, 64	Yes	1997	2004	Positive
2	M, 35	No	2001	2001	Positive
3	F, 40	Yes	1998	2005	Positive
4	M, 61	Yes	2006	2006	Positive
5	M, 60	Yes	2002	2006	Positive
6	F, 62[c]	Yes	1988	2002	Positive
7	M, 24	Yes	1988	1988	Positive
8	F, 48	Yes	1988	1988[e]	Negative
9	M, 30	Yes	1990	1990	Positive
10	M, 33	Yes	2004	2005	Positive
11	M, 35	Yes	2004	2006[d]	Positive
12	F, 43	No	2002	2003	Positive
13	M, 32	No	2007	2007	Positive
14	M, 34	yes	2003	2004	Positive
15	M, 40	No	2007	2007	Negative
16	M, 61	No	2002	2004	Positive
17	M, 64[c]	Yes	1998	2006	Negative
18	F, 42[c]	No	2005	2006	Positive
19	M, 43	No	2003	2006	Positive
20	F, 67[c]	Yes	2005	2005	Positive
21	M, 40	Yes	2003	2005	Negative
22	M, 45	Yes	2004	2006	Positive
23	M, 25	Yes	1989	2004	Positive
24	F, 35	No	2002	2005	Positive
25	F, 49	No	2000	2003	Positive
26	F, 64	Yes	2003	2007	Negative
27	M, 34	No	2005	2006	Positive
28	M, 47	No	2005	2006	Positive

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Results

- **28 out of 93** patient with HNP found to have elevated catecholamines **(30%)**
- **Intra-adrenal paragangliomas** (pheochromocytomas) were identified in 11 out of 28 pts **(39%)**
- **Extra-adrenal paragangliomas** in ***abdomen or pelvis*** were found 6 patients **(21%)**
- **Mediastinal paragangliomas** found in 2 pts **(7%)**
- **In 8 patients** with HNP and increased catecholamine and/or catecholamine metabolite excretion, ***No*** pheochromocytomas or extra-adrenal Paraganglioma identified **(28%).**
  - Uptake of MIBG in the glomus tumor was found in seven out of these 8 patients
- 2% of **SDHD** associated HNP have negative FH of PG

Summary

- Individuals with an ***inherited form of paragangliomas*** have an increased risk to develop ***paragangliomas or pheochromocytomas*** over their lifetime **(around 30%)**
- Hereditary paraganglioma syndrome is due to mutations n one of three genes: **SDHB, SDHC, SDHD** (succinate dehydrogenase subunit B, C, or D)
- Collectively, **SDH mutations are found** in 1-10% of apparently sporadic Paraganglioma and 20-30% of seemingly inherited Paraganglioma
- Individuals with mutations in the **SDHD** gene seem to develop more head and neck tumors. These tumors are more likely to be multifocal
- There seems to be an earlier age of onset for individu with a mutation in the **SDHD** gene, with approximately **73% manifesting the disease by age 40**.
- Individuals with mutations in the **SDHB** gene seem to have more **extra-adrenal abdominal tumors** than those with mutations in the SDHD gene
- Approximately **45%** of individuals with mutations in the SDHB gene will display the disease by age 40

NANETS Recommendations:

- Individuals with hereditary paraganglioma syndrome should have regular screening for signs of paraganglioma development, beginning at age 10.

Screening guidelines

1. **Annual history and physical examination, including blood pressure measurements**
2. **Biochemical analysis every 6-12 months (urine catecholamines, plasma metanephrines)**
3. CT/MRI Imaging (every other year)
   ***SDHD/SDHC*: Head/neck**
   SDHB: Abdomen, thorax, pelvis
4. I-MIBG imaging and/or full-body MRI (every four years)

Back to my patient

- ü **After the surgery >> sever orthostatic hypotension ((currently managed with compression stocking + salt tab))**
- ü **Repeated plasma M&NM were normal**
- ü **Future Plan:**
- v **Biochemical analysis every 6-12 months (urine catecholamines, plasma metanephrines)**
- v **Radiological studies (every other year)**

References

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Thank you

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