Multiple Endocrine Neoplasia Syndromes Demystified

Overview of Diagnosis, Molecular Genetics and Pathophysiology, Screening and Surveillance, and Principles of Management

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1

Disclosure Statement

I have nothing to disclose

2

Learning Objectives

- Understand what the Multiple Endocrine Neoplasia Syndromes (MENs) are and how to diagnose them.
- Understand the pathophysiology responsible for MENs.
- Learn the initial evaluation and workup (from primary care /non-specialist perspective).
- Learn the broad principles of MEN management including the 4 S's: **S**creening, **S**urgery, **S**urveillance, and **S**ynergy (Multidisciplinary Care).

3

Learning Objectives

- **Understand what the Multiple Endocrine Neoplasia Syndromes type 1 is and how to diagnose it.**
- Understand the pathophysiology responsible for MENs.
- Learn the initial evaluation and workup (from primary care perspective).
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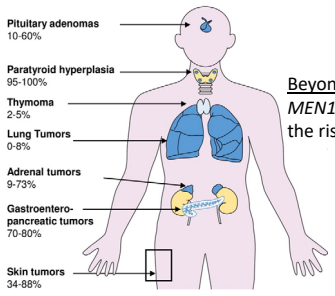
4

MEN1 Overview

- Formerly Wermer Syndrome
- Classic 3 **P**'s – tumors of **p**arathyroid, **p**ituitary and **p**ancreas



Beyond the 3 P's:
MEN1 mutations also increase the risk of cancer in other tissues

Mohr et al. *Endo Related Cancers* 2017

5

Representative Cases From Our Clinic

Case 1:
49F no symptoms
Hyperpara/ parathyroid surgery in 2019. In the interim,

In the interim, sister (age early 40s) had multifocal hyperpara→ MEN1 diagnosis. Subsequently, mother with long-standing history of peptic ulcer disease, hyperpara was also diagnosed with MEN1.

Genetic testing July 2019:
MEN1 variant **c1364T>A (pVal455Glu)** classification of "uncertain significance, heterozygous." **(GeneDx)**

6

Representative Cases from our clinic

Case 2
36M with no prior FH (maybe kidney stones?)
PMH of kidney stones

Recently headaches, erectile dysfunction led to diagnosis of prolactinoma → started on cabergoline.

CLINICAL diagnosis of MEN1.

Interested in genetic testing primarily for benefit of children ages 5,3, and 1.

7

Percentage of MEN1 Patients with Tumors by ~Age 40

TABLE 1. MEN syndromes and their characteristic tumors and associated genetic abnormalities

Type (chromosome location)	Tumors (estimated penetrance)	Gene, most frequently mutated codons
MEN1 (11q13)	Parathyroid adenoma (90%), Enteropancreatic tumor (30–70%), gastrinoma (40%), insulinoma (10%), nonfunctioning and PPoma (20–55%), glucagonoma (<1%), VIPoma (<1%) Pituitary adenoma (30–40%), prolactinoma (20%), somatotropinoma (10%), corticotropinoma (<5%), nonfunctioning (<5%) Associated tumors: adrenal cortical tumor (40%), pheochromocytoma (<1%), bronchopulmonary NET (2%), thymic NET (2%), gastric NET (10%), lipomas (30%), angiofibromas (85%), collagenomas (70%), meningiomas (8%)	*MEN1* 83/84, 4-bp del (~4%) 119, 3-bp del (~3%) 209–211, 4-bp del (~8%) 418, 3-bp del (~4%) 514–516, del or ins (~7%) Intron 4 ss, (~10%)

Thakker et al. *JCEM* Sept. 2012

8

Ways to Establish the Diagnosis of MEN1

CLINICAL
- 2 or more primary MEN1-associated endocrine tumors
  (i.e. parathyroid adenoma, pituitary adenoma)

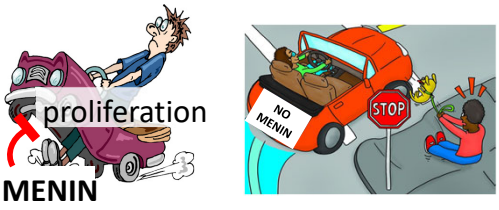
FAMILIAL
- 1 MEN1-associated tumor in 1st degree relative of patient with clinical diagnosis of MEN1.
- Autosomal Dominant inheritance pattern

GENETIC
- Mutation in *MEN1* in asymptomatic individual
- (10% have "de novo" mutations that are NOT inherited)

9

The *MEN1* gene encodes for the protein Menin

- MEN1 is a "tumor suppressor" gene that puts the brakes on growth and proliferation of cells
- Mutations cause "loss of function"

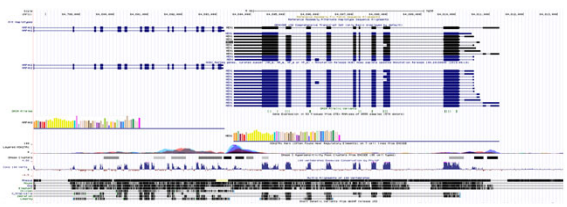


Mutations in MEN1 cause MEN1 and are also responsible for a subset of sporadic endocrine tumors

10

Genetic Testing in MEN1: how good is the test?

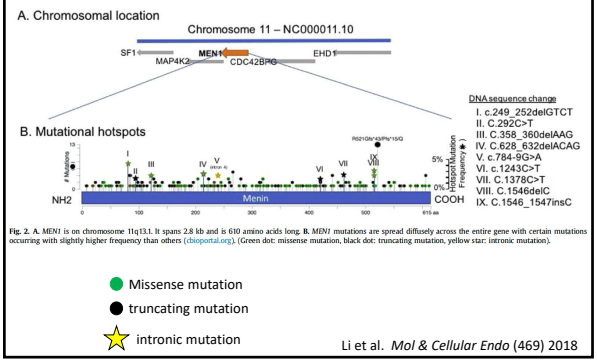
- MEN1 mutations detectable in only **~70-75% of classical MEN1**
- MEN1 (menin) gene spans **9kb** of the genome in 10 exons and encodes for a protein with 610 amino acids.
- This size and location of mutations makes testing difficult



MEN1 gene from UCSC Genome Browser: https://genome.ucsc.edu/cgi-bin/hgGateway

11

Mutations in *MEN1* Are Widely Dispersed

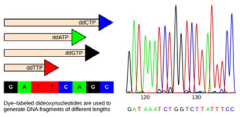


Li et al. *Mol & Cellular Endo* (469) 2018

12

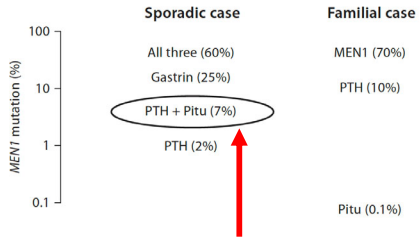
What exactly does MEN1 genetic testing examine?

- Somewhat depends on the Laboratory performing the test.
- E.g. Athena diagnostics "methods":
  - Sanger Sequencing
  - Detects mutations in the ***coding*** sequence of MEN1
  - "at least 10 bases of intronic DNA on either side of each exon containing the highly conserved exon-intron splice junctions were also sequenced"
  - "This method **does not** detect large deletions or insertions … does not detect variants in the regions of the gene not analyzed ie. Promoter, 5'and 3' untranslated regions and introns)."



13

Sporadic Cases meeting clinical MEN1 criteria: *MEN1* mutation detection is low



Meets CLINICAL criteria for MEN1, but only 7% have *MEN1* mutations

Agarwal et al. *Hormone Research* (71) 2009

14

Implications for Screening Family Members

- Whether to screen is a case-by-case decision (get help from genetic counseling!)
- There is little evidence that pre-clinical detection reduces morbidity or mortality in MEN1.
- A pathologic mutation in the affected patient can help exclude family members who do NOT Have the mutation (and don't need cost and stress of surveillance).

15

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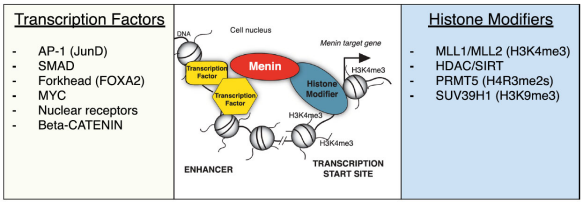
16

What is menin and why do mutations cause disease?

17

Menin is a "Platform" Protein Regulating Gene Expression



Dreijerink et al. *Endo Related Cancers* 2017

18

Menin interacts with transcriptional machinery and also signaling and other proteins

Menin

(1) Transcription activators
c-Myb, MLL1, SMAD 1,3,5, Pem, Runx2, Hlbx9, ER, PPARγ, vitamin D receptor

(2) Transcription repressors
JunD, Sin3A, HDAC, EZH2, PRMT5,NFκB, Sirt1, CHES1

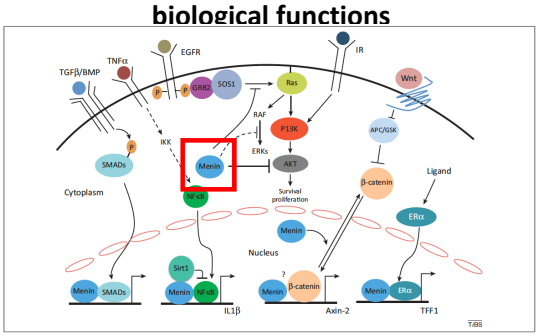
(3) Cell signaling proteins
AKT, SOS1/GEF, β-catenin, SMAD 1,3,5, NFκB, ER, PPARγ, vitamin D receptor

(4) Other proteins
Cell cycle: RPA2, ASK
DNA repair: FANCD2
Cell structure: GFAP, vimentin, NMMHCIIA, IQGAP1
Others: HSP70, CHIP

Maktar et al. *TIBS* 2013

19

Menin regulates and is regulated by many pathways promoting crosstalk across diverse biological functions

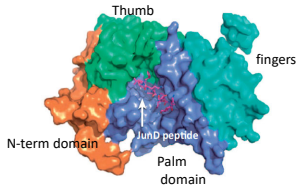


Matkar et al. *TIBS* 2013

20

Still Much Is Unknown

- Menin is expressed in many tissues in the body– why endocrine organs are particularly susceptible to tumors is not well understood.
- Menin function still is not poorly understood.



Maktar et al. *TIBS* 2013; Huang et al. *Nature* 2012

21

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22

Screening Recommendations From MEN1 Experts in the Endocrine Society

TABLE 2. Suggested biochemical and radiological screening in individuals at highrisk of developing MEN1

Tumor	Age to begin (yr)	Biochemical test (plasma or serum) annually	Imaging test (time interval)
Parathyroid	8	Calcium, PTH	None
Pancreatic NET			
Gastrinoma	20	Gastrin (± gastric pH)	None
Insulinoma	5	Fasting glucose, insulin	None
Other pancreatic NET	<10	Chromogranin-A, pancreatic polypeptide, glucagon, VIP	MRI, CT, or EUS (annually)
Anterior pituitary	5	Prolactin, IGF-I	MRI (every 3 yr)
Adrenal	<10	None unless symptoms or signs of functioning tumor and/or tumor >1 cm are identified on imaging	MRI or CT (annually with pancreatic imaging)
Thymic and bronchial carcinoid	15	None	CT or MRI (every 1–2 yr)

Thakker et al. *JCEM* Sept. 2012

These are **Guidelines NOT Rules**... Management still depends on evaluation and discussion with each individual patient, and there is variation in practice even amongst MEN experts.

23

Initial Evaluation for non-specialists

- Ordering a few critical tests can make initial consultation with specialists much more productive.
- Calcium and PTH (parathyroid)
- Prolactin, IGF-1 (pituitary)
- Consider fasting labs for glucose, insulin, other GI/pancreas labs as indicated by testing
- Defer imaging to specialty clinics

24

Surgery is the Cornerstone of MEN1 Therapy

25

How Are MEN1 Patients Best Cared For?

In a MULTIDISCIPLINARY TEAM at CENTERS WITH EXPERTISE IN MEN1 and management of all types of endocrine tumors.
Think Synergy!

- Endocrinologist with expertise in MEN should coordinate care within Multidisciplinary Treatment (MDT)
- Patients with MEN1 should be seen regularly (3-6 months or as clinically indicated)
- Asymptomatic 1st degree relatives screened annually
- Lifelong review at specialty center (ideally the same one)
- Access to MDT specialists: endocrinologists, gastroenterologists, surgical specialists, oncologists, radiologists, clinical geneticists, etc.
- Patients should join a local or national MEN1 registry

Thakker et al. *JCEM* Sept. 2012

26

Back to Our Cases:

- **CASE 1: c1364T>A (pVal455Glu)** "**This variant has not, to our knowledge, been published in the literature as a pathogenic** or benign germline variant…."
- **Should be reported as pathogenic to registries.**

- **Case 2:**
- Labs showed calcium of **11.2** with PTH of **166** (12-88)
- Scheduled for parathyroid surgery with Endocrine Surgery*
- Evaluate for hypopituitarism, optimize prolactinoma treatment.
- Discussion of pros &cons of genetic testing / refer to Genetics.

27

MEN1 Summary:

- MEN1 can be diagnosed with clinical, familial, **or** genetic criteria.
- Inactivating mutations in the *MEN1* gene damage menin's ability to suppress growth and proliferation, promoting tumor development.
- Periodic blood tests and imaging studies should be repeated throughout life to find tumors.
- MEN1 patients should receive care in multidisciplinary centers with expertise across medical and surgical specialties.

28

Brief Interlude

29

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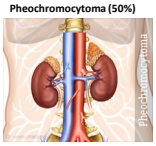
30

MEN2 Overview

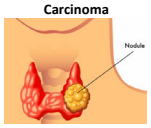
CLINICAL

- Characteristic Tumors:

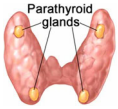
Pheochromocytoma (50%)



Medullary Thyroid Carcinoma



Hyperparathyroidism (to ~30%)



FAMILIAL HISTORY

- Autosomal Dominant

GENETICs

- Caused by mutations in the RET gene on Chromosome 10

31

Representative MEN2 Cases from our clinic

CASE 1:

27 yo white male with no significant PMH.

His mother, age 50, had a thyroidectomy →medullary thyroid CA on pathology. Genetic testing revealed a pathogenic variant of *RET*, consistent with MEN2A.

The patient was seen by the Genetics clinic and found to have the same mutation (C609Y) as his mother.

He was referred to the Endocrine Clinic.

Patient hopes to join Army Reserves soon, is concerned about whether the diagnosis will affect those plans.

Vitals: 98.1, 111/69, HR 75, 80 kg / BMI 22lg/m2

Exam: unremarkable

32

Representative MEN2 Cases from our clinic

CASE 2:
23 yo Hispanic female with no significant PMH.

Toddler son had Hirshprung's disease as an infant; testing revealed a genetic diagnosis of MEN2A

Patient was seen by Genetics and found to have the same mutation (C620Y).

Vitals: 98.6, 121/80, HR 95, 53 kg / BMI 32.2 kg/m2
Exam: unremarkable

33

MEN2 SUBTYPES

MEN2A

- 2 or more specific endocrine tumors (medullary thyroid carcinoma [MTC], pheochromocytoma, or parathyroid adenoma/hyperplasia) in a single individual or in close relatives.

FMTC (Familial medullary thyroid CA)

- Families with 4 or more cases of MTC in the absence of pheochromocytoma or parathyroid adenoma/hyperplasia.

MEN2B

- Early-onset MTC, mucosal neuromas of the lips and tongue, as well as medullated corneal nerve fibers, distinctive facies with enlarged lips, and an asthenic, marfanoid body habitus.

34

Percentage of MEN2 Patients with Tumors by ~Age 40

TABLE 1. MEN syndromes and their characteristic tumors and associated genetic abnormalities

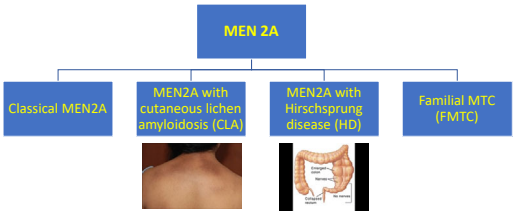
Type (chromosome location)	Tumors (estimated penetrance)	Gene, most frequently mutated codons
MEN2 (10 cen-10q11.2)		
MEN2A	MTC (90%)	*RET*
	Pheochromocytoma (50%)	634, missense
	Parathyroid adenoma (20–30%)	e.g. Cys→Arg (~85%)
MTC only	MTC (100%)	*RET*
		618, missense (>50%)
MEN2B (also known as MEN3)	MTC (>90%)	*RET*
	Pheochromocytoma (40–50%)	918, Met→Thr (>95%)
	Associated abnormalities (40–50%)	
	Mucosal neuromas	
	Marfanoid habitus	
	Medullated corneal nerve fibers	
	Megacolon	

Unlike MEN1, the primary presenting tumor in MEN2 is thyroid CANCER prompting the need for more urgent pace of evaluation and treatment.

Thakker et al. *JCEM* Sept. 2012

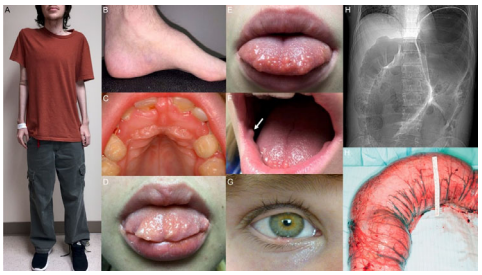
35

Summary of MEN2A



36

MEN 2B



The pathognomonic clinical phenotype of MEN2B: (1) a marfanoid body habitus (A) and other skeletal features including scoliosis (A), pes cavus (B), and high-arched palate (C); (2) thickened lips and neuromas affecting the tongue (D and E), the oral mucosa, (F) the conjunctiva (G), and other mucosal surfaces; (3) ophthalmological signs including ptosis and everted upper eyelids (G); and (4) gastrointestinal problems primarily related to impaired colonic motility due to diffuse intestinal ganglioneuromatosis that can lead to megacolon (H).

37

MEN 2B

- Develop pheochromocytomas but **not** hyperparathyroidism.
- 90% have gastrointestinal symptoms
- **MTC is highly aggressive**
- Narrow window during which thyroid removal may be curative

Mutations
- M918T
- A883F

38

Medullary Thyroid Cancer (MTC)

- Accounts for 5% of all thyroid cancers
- Arises from C-cells in the thyroid

Diagnosis:
- Serum calcitonin levels
- DNA analysis for Mutations
- Ultrasound

Tumor Markers:
Calcitonin
Carcinoembryonic antigen (CEA)

Typically spreads to lymph nodes and subsequently to the liver, lungs, bone and brain.

39

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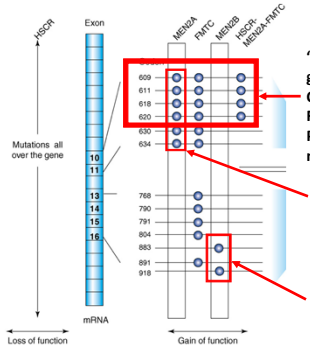
40

Mutations in the *RET* gene underlie MEN2

- RET is an "oncogene" promotes growth/ cancer when active
- Mutations cause "gain of function" and activation of downstream pathways

41

MEN2 / *RET*: strong genotype/phenotype correlations



"Janus" mutations confer both gain and loss of function:
Constituitive RET (MEN2A, FMTC)
Poorly expressed at cell surface mimics loss of function (HSCR)

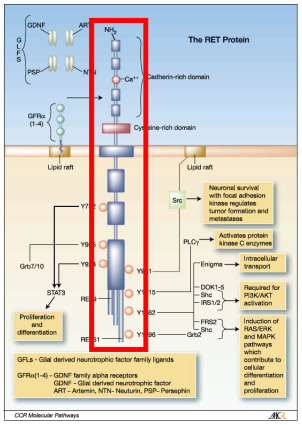
95% of MEN2A mutations Form ligand INDEPENDENT receptor dimerization/ constuitive RET signaling.

MEN2B: increased kinase activity, ATP binding, changes substrate recognition

Plaza-Menacho et al *Trends in Genetics* 2006

42

How RET promotes growth / cancer



Wells & Santoro. *Clin.CA Res* Dec. 2009

43

RET has a STRONG Genotype-Phenotype Correlation (unlike *MEN1)*
A small number of mutations account for the majority of cases

TABLE 4. RELATIONSHIP OF COMMON *RET* MUTATIONS TO RISK OF AGGRESSIVE MTC IN MEN2A AND MEN2B, AND TO THE INCIDENCE OF PHEO, HPTH, CLA, AND HD IN MEN2A

RET *mutation*[a]	*Exon*	*MTC risk level*[b]	*Incidence of PHEO*[c]	*Incidence of HPTH*[c]	*CLA*[d]	*HD*[d]
G533C	8	MOD	+	–	N	N
C609F/G/R/S/Y	10	MOD	+/++	+	N	Y
C611F/G/S/Y/W	10	MOD	+/++	+	N	Y
C618F/R/S	10	MOD	+/++	+	N	Y
C620F/R/S	10	MOD	+/++	+	N	Y
C630R/Y	11	MOD	+/++	+	N	N
D631Y	11	MOD	+++	–	N	N
C634F/G/R/S/W/Y	11	H	+++	++	Y	N
K666E	11	MOD	+	–	N	N
E768D	13	MOD	–	–	N	N
L790F	13	MOD	+	–	N	N
V804L	14	MOD	+	+	N	N
V804M	14	MOD	+	+	Y	N
A883F	15	H	+++	–	N	N
S891A	15	MOD	+	+	N	N
R912P	16	MOD	–	–	N	N
M918T	16	HST	+++	–	N	N

[a]The references for each of the *RET* mutations can be found in the Supplementary Information, where all reported *RET* mutations in MTC are listed.
[b]Risk of aggressive MTC: MOD, moderate; H, high; HST, highest.
[c]Incidence of PHEO and HPTH: + = ~10%; ++ = ~20%–30%; +++ = ~50%.
[d]Y, positive occurrence; N, negative occurrence.

Table from ATA Guidelines for the Management of MTC (*Thyroid*, 2015)

44

Who needs Genetic Testing?

- Sporadic MTC
- First degree relatives of patients with MTC
- Infants or children with clinical features of MEN2B
- Patients with cutaneous lichen amyloidosis

45

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46

Initial Evaluation for non-specialists

- MTC workup: calcitonin, CEA levels.
- Hyperpara eval: Calcium and PTH levels. (hypercalcemia usually mild; vast majority of patients asymptomatic)
- **Evaluate for pheochromocytoma BEFORE considering thyroid surgery!**
- Consult with or defer imaging choice to specialty clinics

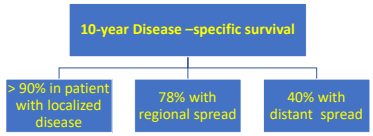
47

As with MEN1, Surgery is the Cornerstone of MEN2 Therapy

48

How do we manage MTC?

- Thyroidectomy for MTC (risk) is the initial treatment of choice
- Thyroidectomy in high-risk patients is recommended in the first few year of life
- The strongest predictor of survival is stage of disease at diagnosis:



49

Timing of Prophylactic Thyroidectomy

Subtype	Clinical Features	Age at Presentation (Decade)	Timing of Surgery
Men 2A	MTC Pheo Hyperpara	3rd	<5 years
MEN2B	MTC Pheo Marfanoid Mucosal Neuromas	1st or 2nd	<1 year
FMTC	MTC	4th	5-10 years

50

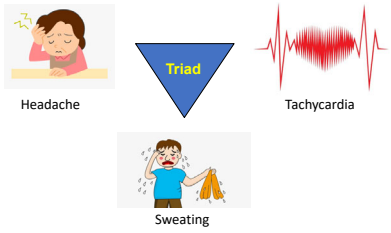
How do we manage MTC after surgery?

- **MULTIDISCIPLINARY APPROACH:**
- Calcitonin levels are monitored postoperatively
- Imaging as necessary / indicated by pathology results.
- Surgery for persistent or recurrent disease.
- Consider chemotherapy and Radiation Therapy

51

Pheochromocytoma

Adrenaline producing tumors of the adrenal glands



52

Diagnosis and Management of Pheochromocytoma

- Measure plasma or urinary fractionated metanephrines
- CT scan or MRI are used to locate the tumor
- Screening in High risk patients should begin at age 11
- **Critical to rule out before any interventional procedures (Avoid triggering a crisis!)**
- Should be resected before MTC if both are present
- Surgical resection (by endocrine surgery, urology, or general surgery depending on local specialist experience)

53

Our MEN2A Patients:

Case 1: C609Y mutation thought to be lower risk for pheo; some don't even routinely screen these patients.

To our surprise…..

- Plasma normetanephrines **8.2** (<0.9)
- Plasma metanephrines **1.1** (<0.5)
- Calcitonin 7, CEA 0.8 (both wnl)

- Dec 2019 Lap L adrenalectomy: **pheo 4.9 cm** greatest dimensions
- Feb 2020 total thyroidectomy: Path **NEGATIVE** for MTC

54

Our MEN2A Patients:

Case 2: C620Y mutation thought to be moderate risk for MTC, low risk for PHEO.

Recommended:

prophylactic thyroidectomy

Genetic testing of 3-year-old daughter

55

MEN2 Summary:

- Both gain and loss of function mutations in *RET* cause Hirschsprung's, MEN2A, MEN2B and FMTC.
- There is a strong genotype-phenotype correlation. The specific mutation is usually highly predictive and useful for clinical decision making.

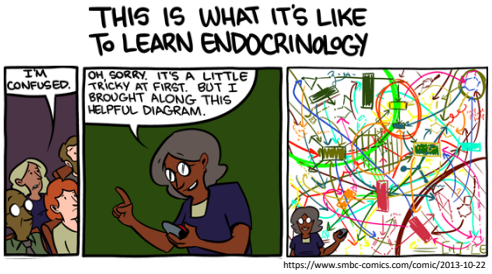
56

MEN1 and MEN2 Summary & Conclusions

- Both are rare familial diseases but can present as de novo or sporadic mutations.
- Both require surgical intervention and subsequent screening and surveillance
- Both should receive care in multidisciplinary centers with expertise across medical and surgical specialties, preferably coordinated by endocrinologists who have experience with patients with the disorders.
- MEN2 has a strong genotype/phenotype correlation; MEN1 does not.

57

The End



You made it!

Thank you

58

Questions?

- Feel free to contact me:

- Ronadip Banerjee
- rbanerjee@uabmc.edu

59

Selected References and Resources

- Clinical Practice Guidelines for Multiple Endocrine Neoplasia Type 1 (MEN1) *JCEM* 2012
- Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma. *Thyroid* 25:6, 2015.

- American Multiple Endocrine Neoplasia Support http://amensupport.org/

60

Acknowledgements

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MEN patients and families

61