SIBO and NETs

Rahm Makan

Small intestinal Bacterial overgrowth (SIBO) Definition

- >10000 CFU per ml of colonic bacteria in the small intestine (gram neg or anaerobes)
- resulting in intestinal or extra-intestinal manifestations.

Innate protection

- Protective mechanisms against SIBO
  - Gastric acid
  - Intestinal motor activity
  - Ileocaecal valve
  - Mucous layer
  - Immunoglobulins
  - Bacteriostatic properties of pancreatic, billiary and intestinal secretions.

Pathogenesis

- Mucosal injury
  - Due to bacteria or toxins/metabolites
  - Results in loss of brush border enzymes and enhanced mucosal permeability
  - Inflammatory response

Pathogenesis

- Competition for nutrients
  - Consumption of
    - Protein
    - B12 and formation of cobamides
    - Thiamine
    - Nicotinamide

Pathogenesis

- Bacterial metabolism
  - Fermentation
  - Deconjugation of primary bile acids
  - Synthesis of
    - Vitamin k
    - Folate
    - Lactic acid
    - Alcohol
    - Acetaldehyde

Aetiology

- Intestinal dysmotility
  - Autonomic neuropathy
  - Hypothyroidism
  - Acromegaly
  - Drugs – opiods, tca, anticholinergics
  - Muscular dystrophy
  - Systemic sclerosis

Aetiology

- Altered anatomy
  - Blind loops
    - Surgery – billroth II, roux en y,
    - Strictures – Crohns, radiation, surgery
    - Ileocaecal valve resection
    - Gastro colic or jejunocolic fistulas
- Hypochlorhydria
- Immune deficiency
- Advanced age
- Cystic fibrosis
- Chronic pancreatitis
- Liver disease

Clinical features

- Non-specific symptoms/signs
  - Gas, bloating, flatulence, abdominal discomfort, diarrhoea,
  - Due to carbohydrate malabsorption
- Specific symptoms/signs
  - Steatorrhoea, weight loss, vit b12 deficiency, iron deficiency, oxalate nephrolithiasis
  - Due to fat malabsorption
  - Hair loss, brittle nails, dry skin, muscle loss, edema
  - Due to protein malabsorption

Diagnosis

- Controversial
- Small bowel aspirate and culture
  - Jejunal aspirate
  - Breath testing
    - Bile acid
    - Xylose
    - Hydrogen and methane
    - Breath with orocaecal scintigraphy
    - Cholyl PABA, Urinary indican

Before a breath test

- Avoid antibiotics, laxative and colon cleansers for 4 weeks prior to test.
- Avoid complex carbohydrates and dairy products on the day
- Fast for 8 hours prior to the test
- Avoid smoking, sleeping, exercising 30min prior to and during the test.
- Consider using a mouthwash with chlorhexidine prior to the test.

Conducting the test

- 50g of glucose in 200mls with baseline breath sample
- Repeat sample every 15min for a total of 180min

- An increase of more than 20ppm hydrogen is diagnostic of SIBO

Confounding factors

- False negative – species of bacteria
- Transit time
- Carbohydrate malabsorption
- Oral microbial contamination
- Diet, smoking and exercise
- Flat line curve
- Elevated baseline

Treatment Principles

- Correct underlying causative disease process
  - Prokinetics
  - Stop drugs reducing intestinal motility
- Address nutritional deficiencies
  - Carbohydrate restriction
  - Low FODMAP
  - Fat restriction
  - Elemental diet
- Modifying of altered microbiota
  - Oral antibiotics
  - Statins

Antibiotics

- Amoxicillin-Clavulanate
- Ciprofloxacin
- Doxycycline
- Metronidazole
- Neomycin
- Norfloxacin
- Rifaximin
- Tetracycline
- Trimethoprim/Sulfamethoxazole

NETs

Neuroendocrine Tumours

NETs

- Functional
- Non-functional

Incidence

- Autopsy 8.4 per 10 000
- Pancreatics NETs account for 1-10% of all pancreatic tumours

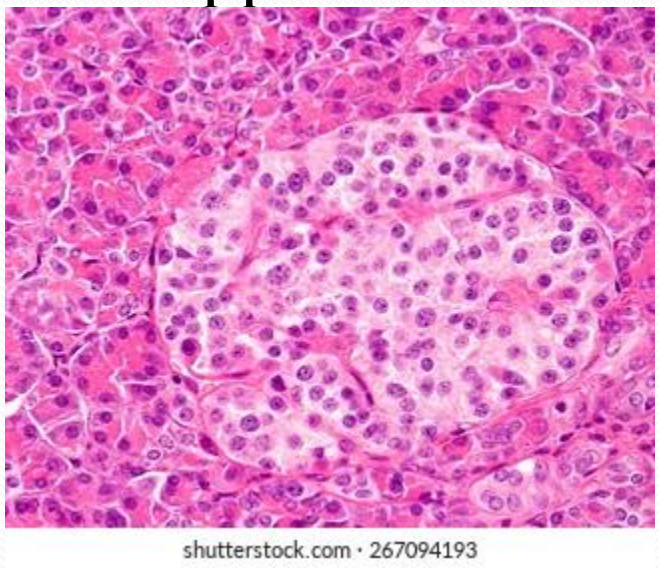
Types of NETs

- Insulinoma
- Gastrinoma
- VIPoma
- Glucagonoma
- GRFoma
- ACTHoma
- Carcinoid
- Rennin, EPO, LH, CCK

Origin

- Neural crest cells
  - Enterochromaffin cells
  - Islets of langerhans

Have a characteristic appearance of dense granules



Classification

- Grade = proliferative activity of the tumour
  - Ki-67 index
- Differentiation = extent to which tumour morphology resembles endocrine cells of origin.

- Malignancy can only be determined by metastases and local tissue invasion – in well differentiated tumours

TABLE 34.2A WHO Classification for GI NETs: 2010

Differentiation	Grade	WHO Grading	WHO Nomenclature
Well differentiated	Low (G1)	<2 mitoses/10 HPF and <3% Ki67 index	NET grade 1
	Intermediate (G2)	2–20 mitoses/ 10 HPF or 3%-20% Ki67 index	NET grade 2
Poorly differentiated	High	>20 mitoses/10 HPF or >20% Ki67 index	Neuroendocrine carcinoma, grade 3 (large-cell or small-cell type)

HPF, High-powered fields; *NET*, neuroendocrine tumors; WHO, World Health Organization.

TABLE 34.2B WHO Classification for Pancreatic NETs: 2017

Differentiation	Grade	WHO Grading	WHO Nomenclature
Well differentiated	Low (G1)	<2 mitoses/10 HPF and <3% Ki67 index	NET grade 1
	Intermediate (G2)	2–20 mitoses/10 HPF or 3%-20% Ki67 index	NET grade 2
	High (G3)	>20 mitoses/10 HPF or >20% ki-67 index	NET grade 3
Poorly differentiated	High	>20 mitoses/10 HPF or >20% Ki67 index	Neuroendocrine carcinoma, grade 3

HPF, High-powered fields; *NET*, neuroendocrine tumors.

Genetics of pNETs

- MEN1 43% of pNETs
- DAXX or ATRX in 43% of pNETs
- mTOR 14%

Inherited Syndromes

TABLE 34.3 Inherited GI Neuroendocrine Tumor Syndromes

Syndrome	Prevalence/10^5	Genetic Defect(s): Altered Protein(s)	NET Frequency	Types of pNET
Multiple endocrine neoplasia type I (MEN-I)	1-10	11q13: Menin, a 610–amino acid nuclear protein that interacts with pathways involved in cell growth, cell cycle regulation, genomic stability, and apoptosis	pNETs 80%-100% (microscopic), 20%-80% (clinical) Carcinoids: gastric (15%-35%), pulmonary (0%-8%), thymic (0%-8%)	NF-pNETs: 80%-100% microscopic; 0%-20% large) Functional pNETs: Gastrinoma (54%) Insulinoma (18%) Glucagonoma (3%) VIPoma (3%) GRFoma (<1%) SSoma (<1%)
von Hippel–Lindau Disease (VHL)	2-3	3p25: pVHL, a 232–amino acid protein that interacts with transcriptional factors that down-regulate HIF and VEGF	10%-17% (pNETs)	NF-pNETs: 98% Functional: 2%
Neurofibromatosis-1 (NF1, von Recklinghausen disease)	20-25	17q11.2: Neurofibromin, a 2484–amino acid protein that has Ras GTPase activity, binds microtubules, regulates mTOR growth, and induces cell cytoskeleton changes	0%-10% (duodenal carcinoids) Rare pNETs	SSomas
Tuberous sclerosis (Bourneville disease)	10	9q34 *(TSC1)* and 16p13 *(TSC2)*: Hamartin (1164–amino acid protein and tuberin (1807–amino acid protein), which interact with the PI3K signaling cascade that regulates mTOR growth, GTPase activity affecting cell growth, energy regulation, response to hypoxia, and nutrients	Uncommon	NF-PETs > functional pNETs

GRF, Growth hormone-releasing factor; *GTP*, guanosine triphosphate; *HIF*, hypoxia-inducible factor; *mTOR*, mammalian target of rapamycin; *pNET*, pancreatic neuroendocrine tumor; *NF*, nonfunctional; *SS*, somatostatin; VEGF, vascular endothelial growth factor.

MEN1 and NETs

- MEN1 –
  - Hyperparathroidism
  - pancreaticoduodenal NETs and
  - pituitary adenomas

  Chromosome 11q13 codes for menin

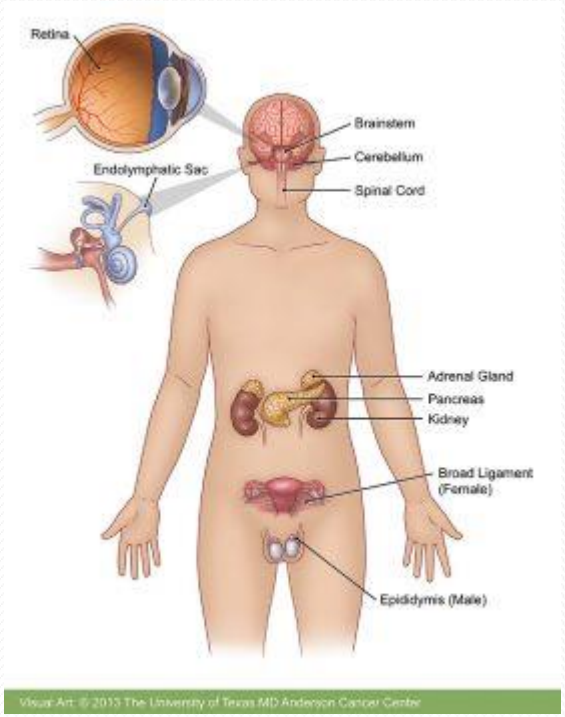
  Knudson 2 hit hypothesis.

Important

- Screen all patients with NETs for MEN

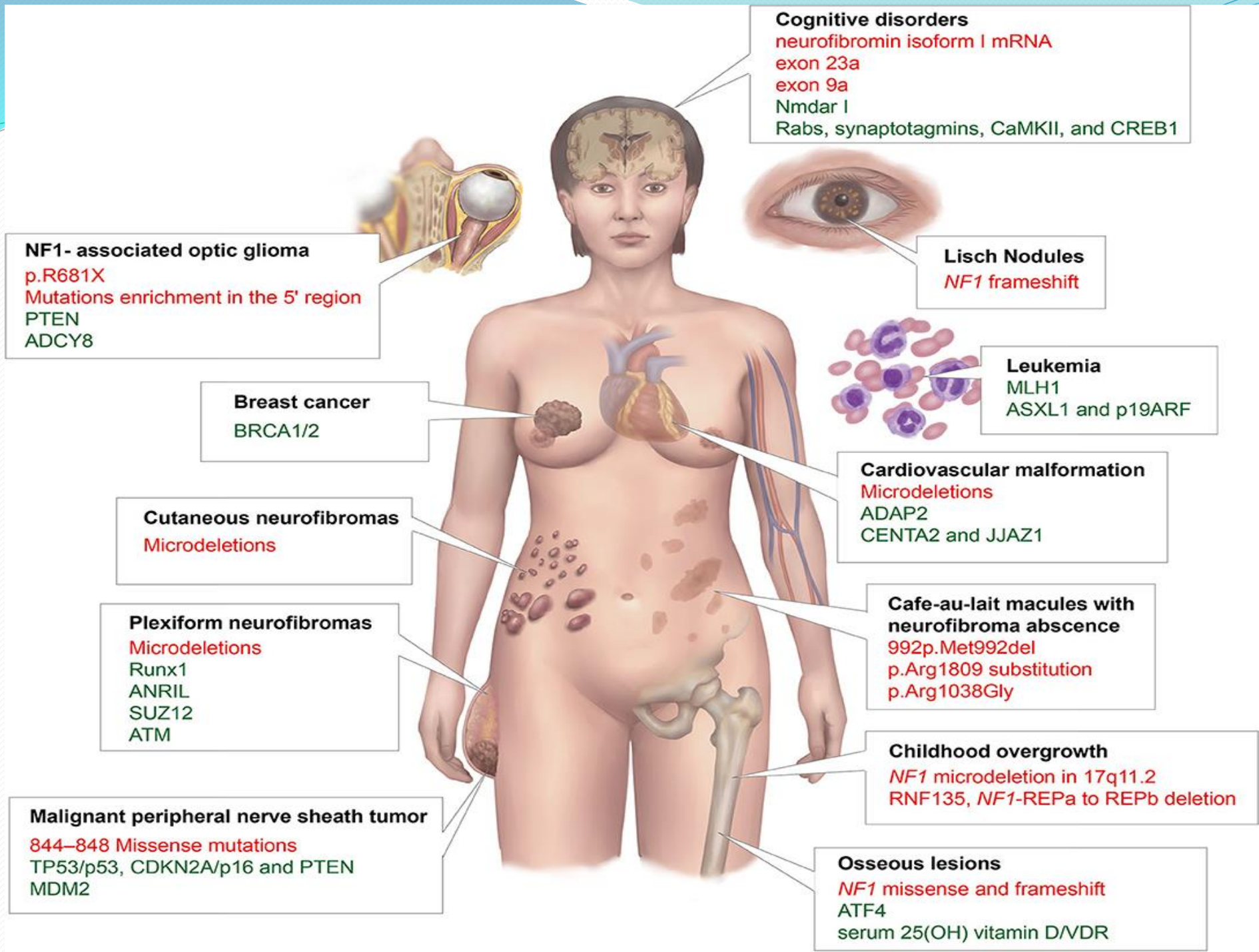
Von-hippel Lindau disease (VHL)

- Chromosome 3p25 that encodes pVHL protein
- 98% of pNETs are asymtomatic and non-functional



Neurofibromatosis Type 1

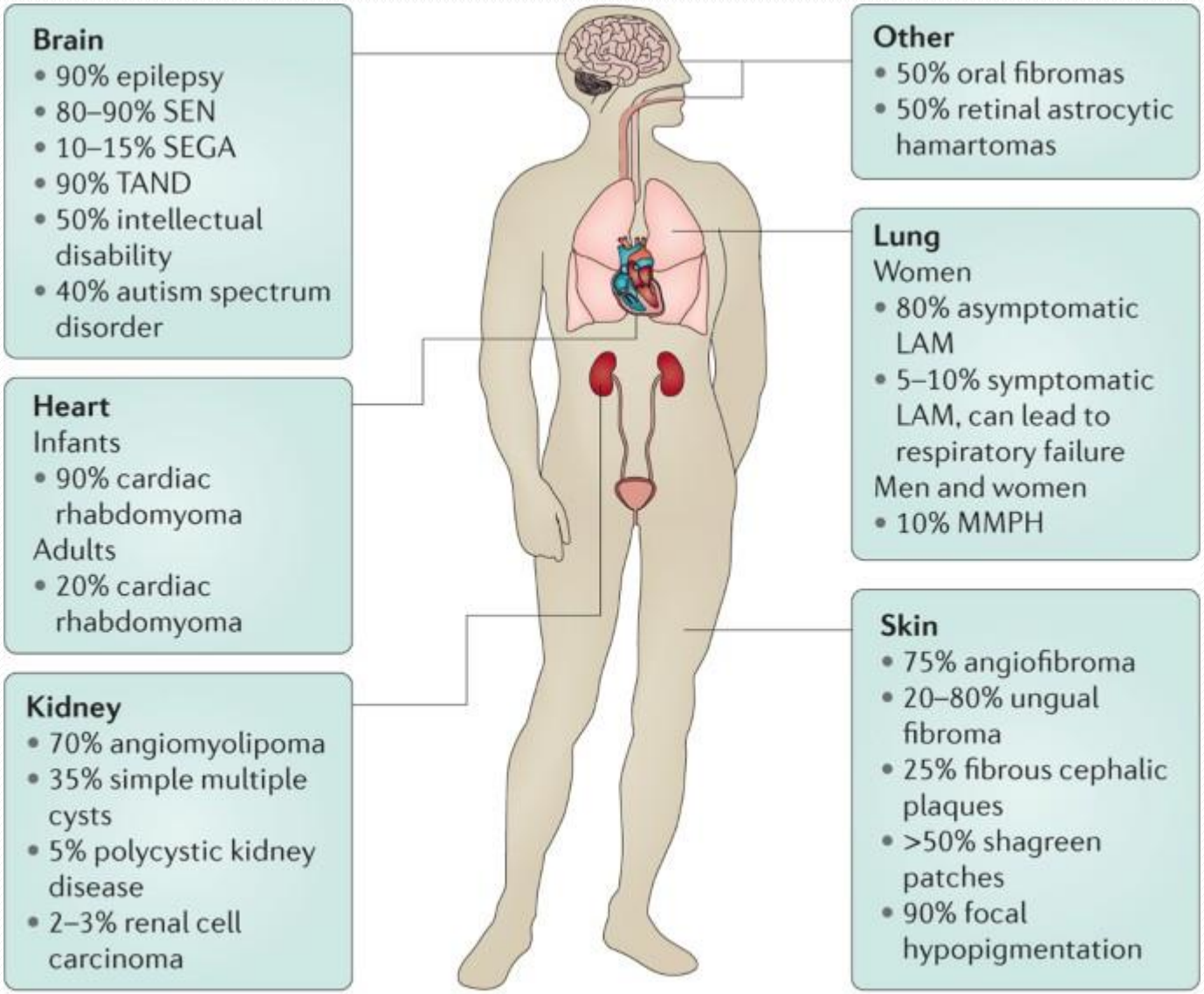
- Chromosome 17q11.2
- Encodes neurofibromin
- Upto 10% of patients develop carcinoid GI NET in periampullary region of duodenum.


Cognitive disorders
neurofibromin isoform I mRNA
exon 23a
exon 9a
Nmdar I
Rabs, synaptotagmins, CaMKII, and CREB1
NF1- associated optic glioma
p.R681X
Mutations enrichment in the 5' region
PTEN
ADCY8
Lisch Nodules
NF1 frameshift
Leukemia
MLH1
ASXL1 and p19ARF
Breast cancer
BRCA1/2
Cardiovascular malformation
Microdeletions
ADAP2
CENTA2 and JJAZ1
Cutaneous neurofibromas
Microdeletions
Plexiform neurofibromas
Microdeletions
Runx1
ANRIL
SUZ12
ATM
Cafe-au-lait macules with neurofibroma abscence
992p.Met992del
p.Arg1809 substitution
p.Arg1038Gly
Childhood overgrowth
NF1 microdeletion in 17q11.2
RNF135, NF1-REPa to REPb deletion
Malignant peripheral nerve sheath tumor
844–848 Missense mutations
TP53/p53, CDKN2A/p16 and PTEN
MDM2
Osseous lesions
NF1 missense and frameshift
ATF4
serum 25(OH) vitamin D/VDR

Tuberous Sclerosis

- Harmartic = TSC1
- Tuberin = TSC2

- 4% of patients with TSC2 have pNETS

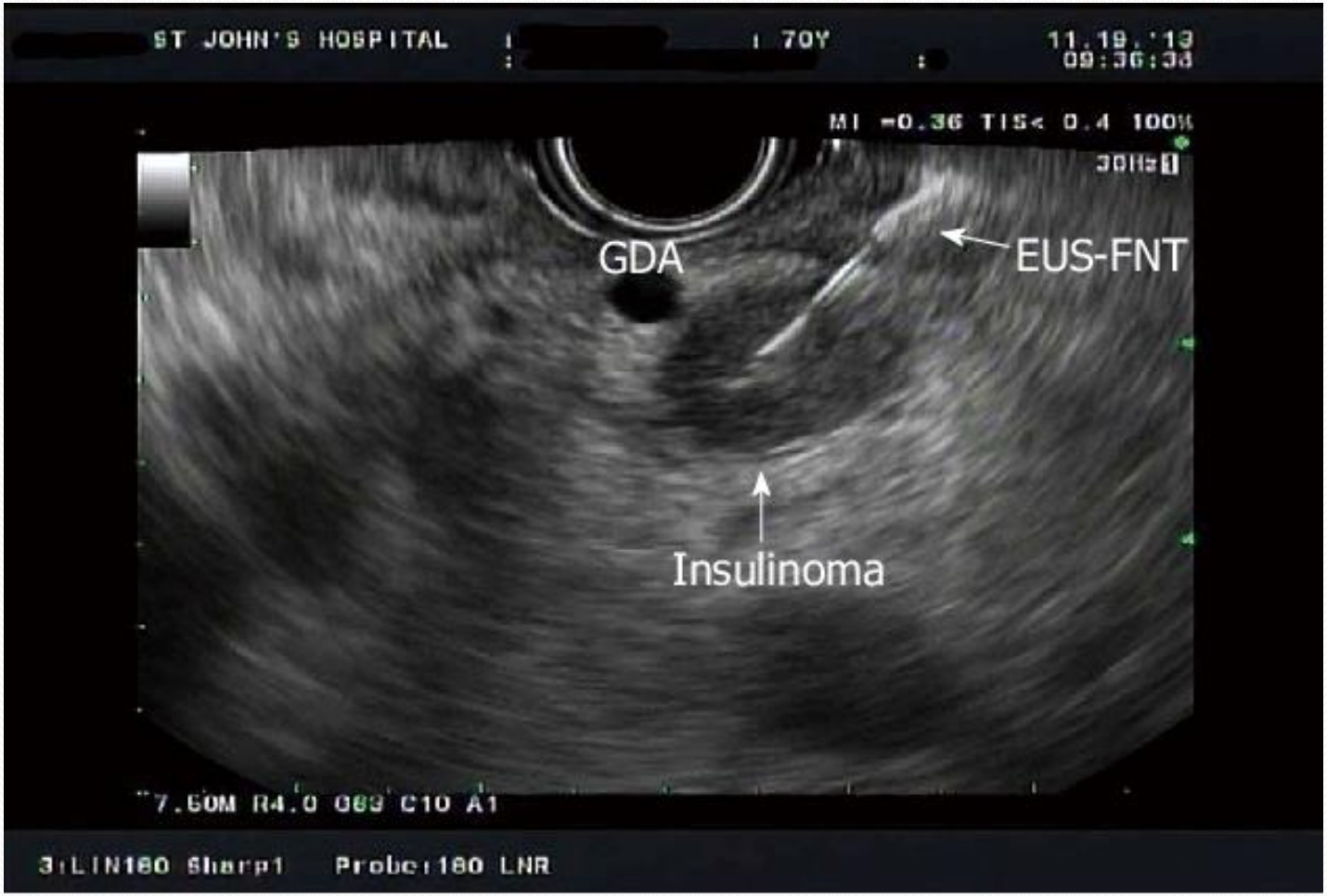

Brain
• 90% epilepsy
• 80–90% SEN
• 10–15% SEGA
• 90% TAND
• 50% intellectual disability
• 40% autism spectrum disorder
Heart
Infants
• 90% cardiac rhabdomyoma
Adults
• 20% cardiac rhabdomyoma
Kidney
• 70% angiomyolipoma
• 35% simple multiple cysts
• 5% polycystic kidney disease
• 2–3% renal cell carcinoma
Other
• 50% oral fibromas
• 50% retinal astrocytic hamartomas
Lung
Women
• 80% asymptomatic LAM
• 5–10% symptomatic LAM, can lead to respiratory failure
Men and women
• 10% MMPH
Skin
• 75% angiofibroma
• 20–80% ungual fibroma
• 25% fibrous cephalic plaques
• >50% shagreen patches
• 90% focal hypopigmentation
Nature Reviews | Disease Primers

Functional Tumours

- Insulinomas
- Gastrinomas
- VIPomas
- Glucagonomas
- Somatostatinomas

Insulinomas

- Occur in pancreas
- Exclude MEN-1
- 5-16% are malignant, 60% women
- Mets to liver or LN
- Fasting hypoglycaemia – Whipple triad
- Elevated pro-insulin vs insulin, therefore low c-peptide
- Insulin: glucose ratio >0,3 (µU/ml:mg/dl) - measure @hypoglycaemic episode


ST JOHN'S HOSPITAL
70Y
11.19.'13
09:36:38
MI =0.36 TIS< 0.4 100%
30Hz
GDA
EUS-FNT
Insulinoma
7.6CM R4.0 C10 A1
3:LIN180 Sharp1
Probe:180 LNR

Insulinoma Treatment

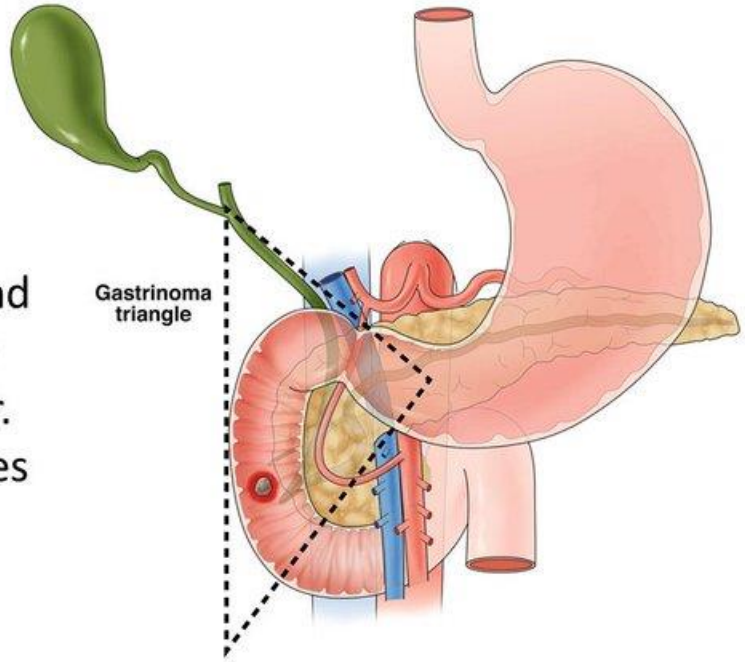
- Control hypoglycaemia – Low GI snacks
- Locate tumour and resect
- PET – somatostatin receptor
- Diazoxide – thiazide
- Somatostatin
- Everolimus

Gastrinoma

- Zollinger Ellison syndrome
- Excessive gastric acid secretion
  - GERD
  - PUD – usually duodenal ulcer
  - Diarrhoea
- 56% in first part of duodenum usually <1cm
- Hepatic mets – pancreatic source lesion>3cm
- PPIs may lead to false diagnosis
- Usually H.pylori negative
- May have personal or FH of MEN1
- Gastrinoma triangle

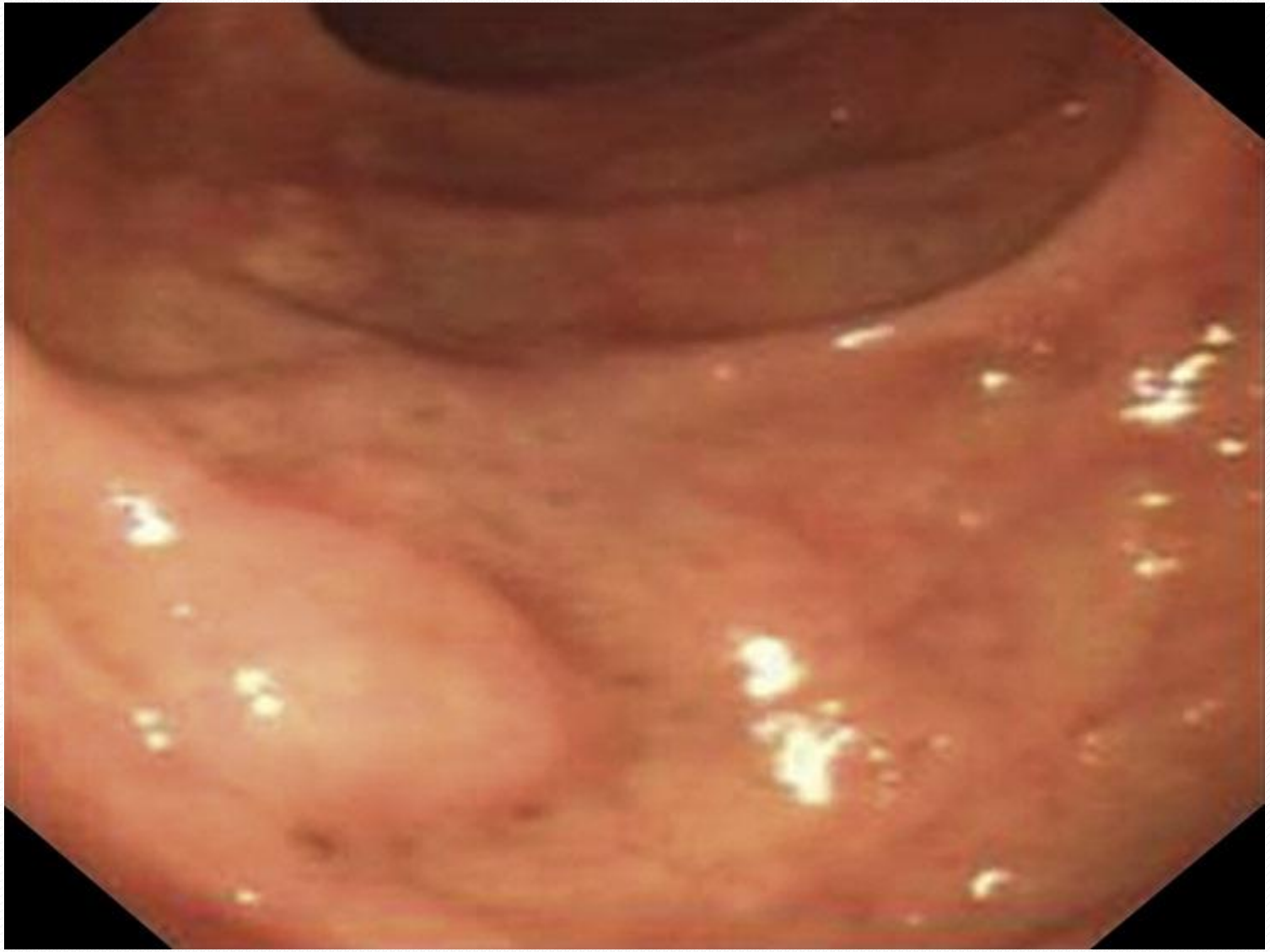
Gastrinoma Triangle

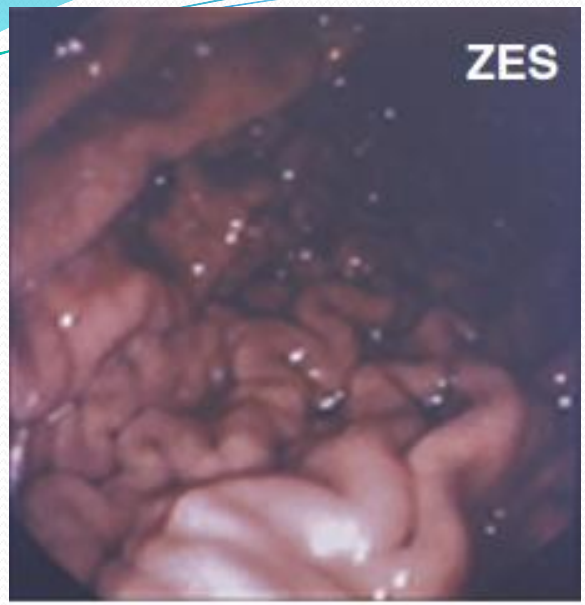
The majority of gastrinomas are found within this triangle first described by Dr. Stabile and colleagues in 1984.



Stabile, B, et. al. Am J Surg. 1984.

Metz, DC. Clin Gastroneterol Hepatol. 2012.





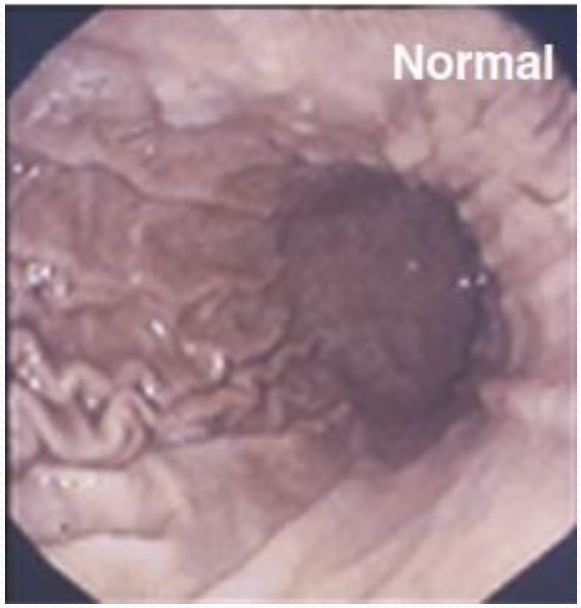


TABLE 34.6 Clinical and Laboratory Features in Patients With ZES

	NIH	Range in Literature
CLINICAL FEATURES		
Average age of onset (years)	41	41-53
Average duration of symptoms (years)	5.2	3.2-8.7
Male gender (%)	56	44-70
Abdominal pain (%)	75	26-98
Diarrhea (%)	73	17-73
History of confirmed PUD (%)	71	71-93
Heartburn (%)	44	0-56
Nausea (%)	30	8-37
Vomiting (%)	25	26-51
Bleeding (%)	24	8-75
MEN-I (%)	22	10-48
Esophageal stricture (%)	4	4-6
GI perforation (%)	5	5-18
LABORATORY FEATURES (%)		
Fasting hypergastrinemia (%)	99	96-100
Positive secretin test (>120 pg/mL increase) (%)	94	94
BAO >15 mEq/hr (no prior gastric surgery) or >5 mEq/hr (prior gastric surgery) (%)	93	43-100

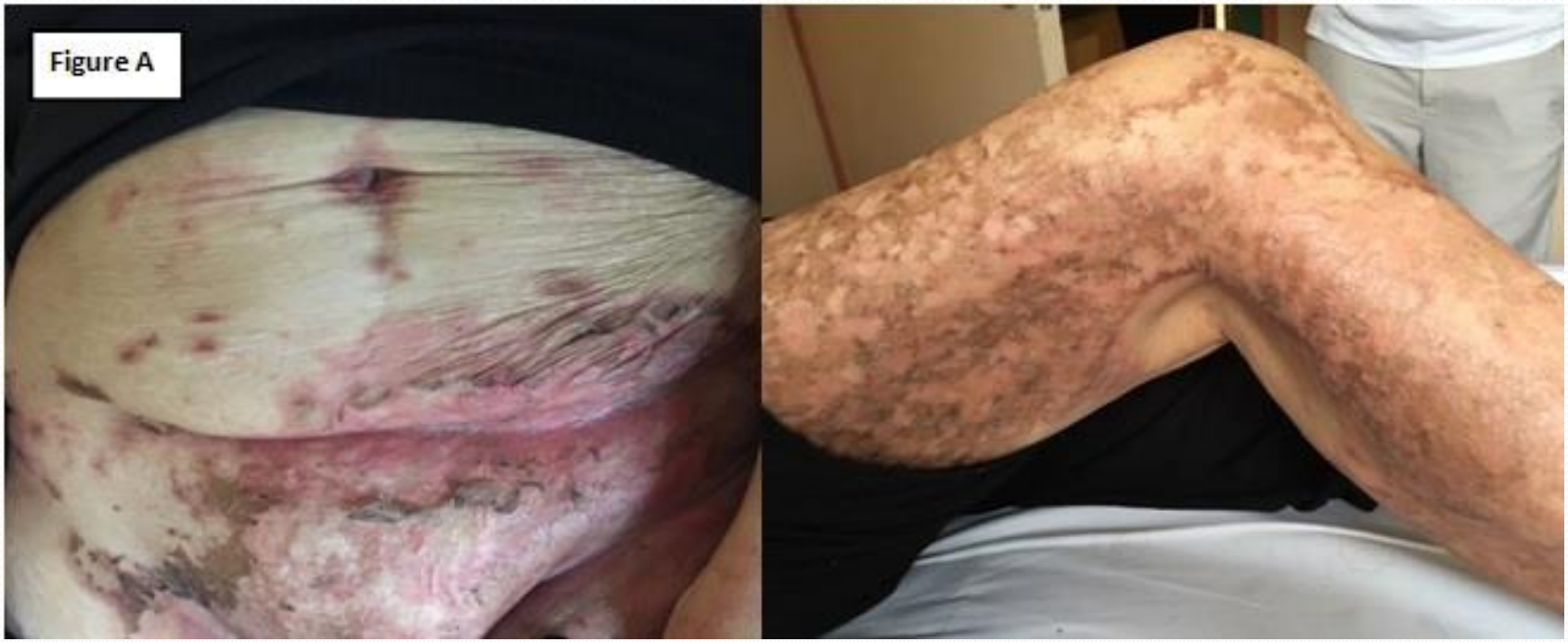
Gastrinoma treatment

- Control acid hypersecretion
  - PPI 60mg / day omeprazole for ZES
  - 60 mg bd for MEN1/ZES
- Curative resection attempted if no liver mets and no MEN1
- Poor surgical outcomes and high rate of recurrence in MEN1/ZES

Glucagonoma

- Secrete glucagon, age 50-70
- Hyperglycaemia, weightloss, rash
- Paraneoplastic skin manifestation
  - Necrotising migratory erythema
  - May be present for years before the tumour is found
- Most often in pancreas
- Mets to liver, LN, bone

- https://doi.org/10.1080/16089677.2020.1793487



Glucagonoma

- Diagnosis
  - Skin rash
  - Increased glucagon levels
  - Diabetes +/-
- Treatment
  - Nutritional optimisation
  - Somatostatin
  - Surgical resection

VIPoma

- Vasoactive intestinal polypeptide, age 42-51
  - Water diarrhoea, hypochlorhydria, achlorhydria, hypokalaemia, volume depletion
- pNET in tail of pancreas
- 50% produce other hormones
  - Glucagon, somatostatin, insulin, gastrin

TABLE 34.7 Clinical and Laboratory Features in Patients With Glucagonoma or VIPoma Syndromes

Glucagonoma	VIPoma
CLINICAL FEATURES (%)	
Dermatitis (54-90)	Secretory diarrhea (89-100)
Diabetes/glucose intolerance (22-90)	Volume depletion (44-100)
Weight loss (56-96)	Weight loss (36-100)
Glossitis/stomatitis/cheilitis (29-40)	Abdominal cramps, colic (10-63)
Diarrhea (14-15)	Flushing (14-34)
Abdominal pain (12)	
Venous thromboembolism (12-35)	
Psychiatric disturbance (uncommon)	
LABORATORY FEATURES (%)	
Anemia (34-85)	Hypokalemia (67-100)
Hypoaminoacidemia (26-100)	Hypochlorhydria (34-72)
Hypocholesterolemia (80)	Hypercalcemia (41-50)
Renal glycosuria (unknown)	Hyperglycemia (18-100)

VIPoma

- Diagnosis
  - Large volume diarrhoea that persists with fasting
  - Raised VIP level
- Treatment
  - Rehydrate and replace electrolytes
  - Somatostatin
  - Surgery once stable

Carcinoids

Carcinoids (GI)

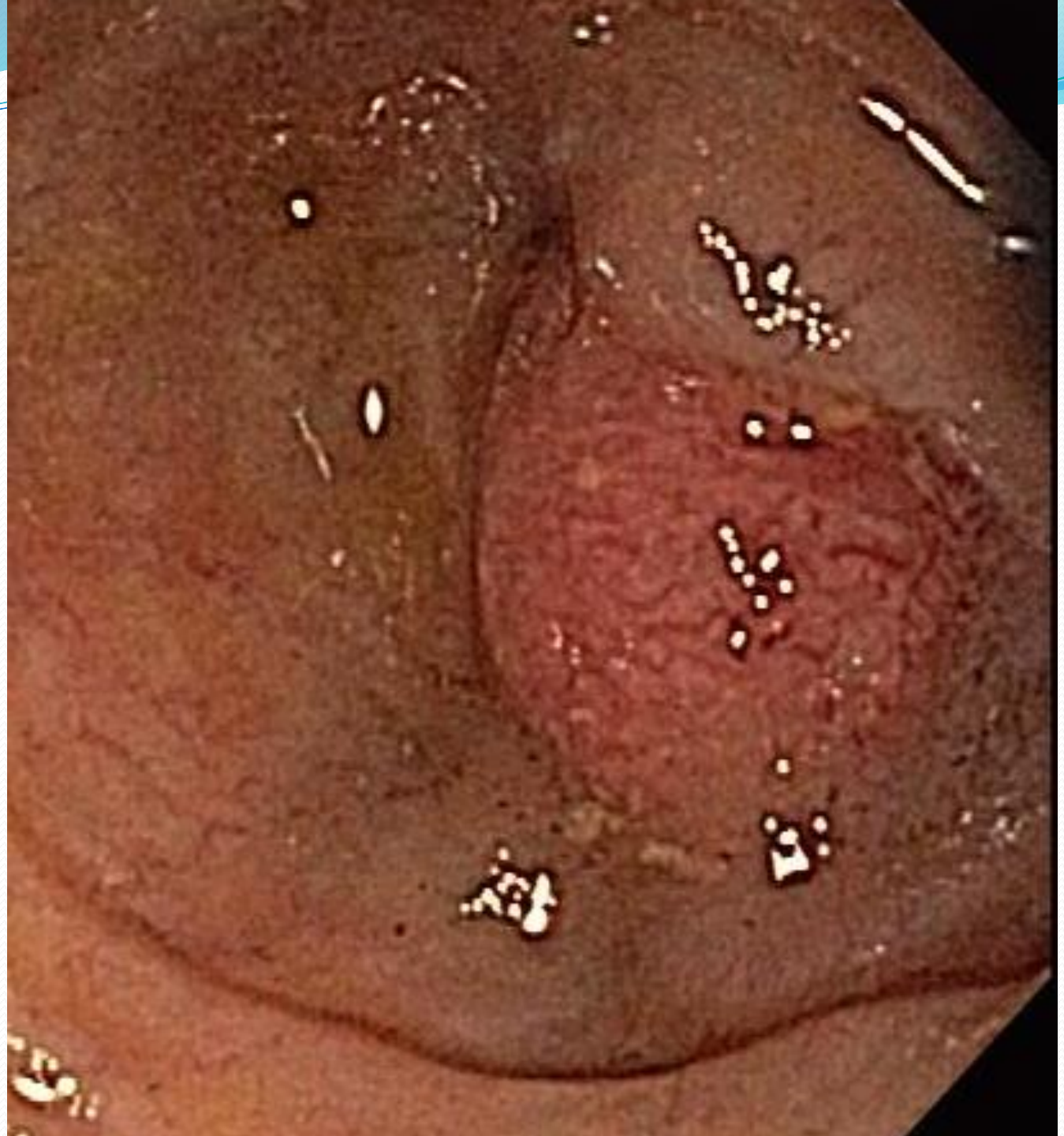
- GI NETS 70% of all carcinoid tumours
- Gastric NETs
  - Type 1– small, multiple, occur in patients with atrophic gastritis
  - Type 2 – occur in MEN1/ZES
  - Type 3 – not asso with hypergastrinaemia, solitary, large and infiltrating

Carcinoid (GI) managment

- <1cm T1 and T2
  - EMR or traditional polypectomy
- 1-2cm T1 or T2
  - EUS to assess dept
  - Polypectomy
  - If high Ki-67 or >2cm then surgical wedge resection
- Type 3 requires imaging before surgical mx
- Somatostatin can cause reduction in size.

Carcinoids (Small intestinal) SI NETS

- Age >60
- Rare familial inheritance – Chromosome 18,Autosomal dominant
- 70-87% in the ileum, usually <1cm
- Mets often occur
- Cholecystectomy at the time of surgery
  - SSA cause gallstones and billiary sludge



Appendiceal NETs

- 3-9 NETs for every 1000 appendicectomies
- If incidental NET is found <2cm then post operative imaging is not recommended.
- Lesions >2cm require radiographic imaging .

Rectal NETs

- >60 years of age
- 1 in every 1500-2500 colonoscopies/proctoscopies
- <1cm tend not to metastasize
- >2cm – treat like rectal adeno CA

Duodenal and ampulla of Vater NETs

- 0,19/100000
- Asso with NF1
- Types
  - Gastrinoma 48-66%
  - Somatostatinoma 15-43%
  - Non functioning 19 – 27%
  - Gangliocytic paraganglionoma <2%
  - Poorly differentiated <3%

Colonic NETs

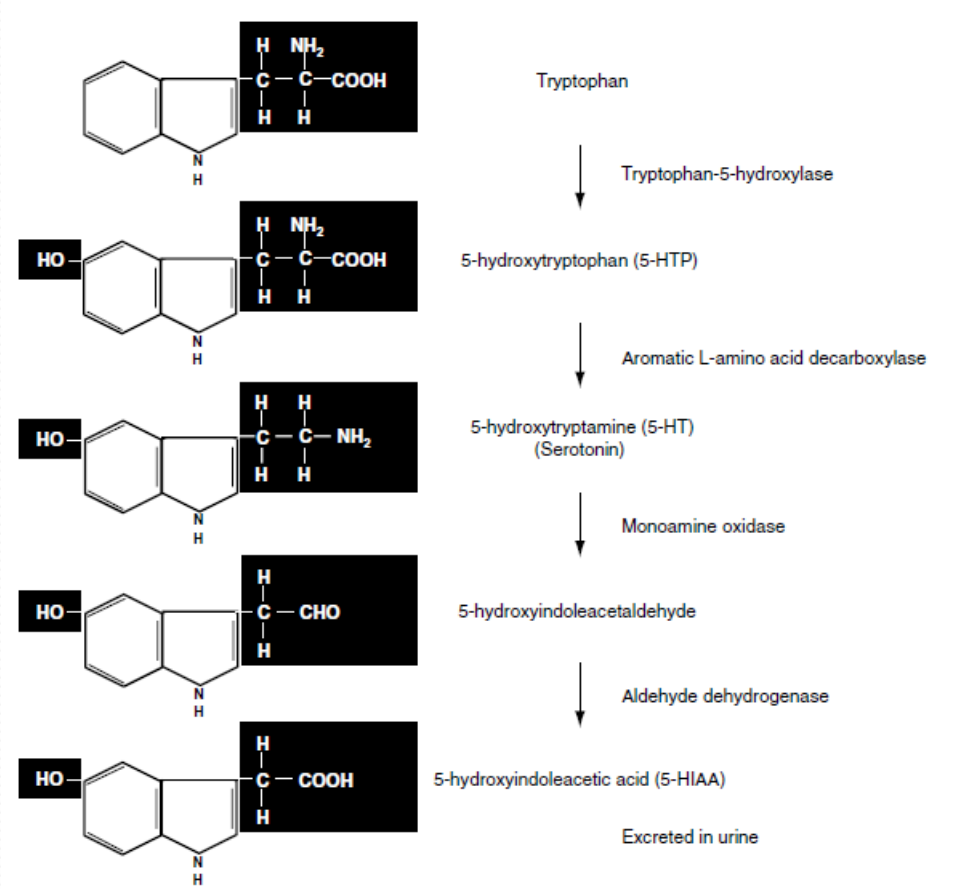
- Age 55-65yo
- 0.06 to 0.19/ 1 000 000
- Often large with mets, >5cm
- Surgical treatment with lymphadenectomy

Carcinoid syndrome

- Occurs when sufficient concentration of hormonal products reach the blood.
- Clinical features
  - Flushing
  - Diarrhoea
  - Carcinoid heart disease TR/PR
  - Wheezing/asthma
  - Pellagra

Carcinoid syndrome types

- Typical
- Atypical – tumour is deficient in enzyme
  - Aromatic L-amino acid decarboxylase


Tryptophan
Tryptophan-5-hydroxylase
5-hydroxytryptophan (5-HTP)
Aromatic L-amino acid decarboxylase
5-hydroxytryptamine (5-HT)
(Serotonin)
Monoamine oxidase
5-hydroxyindoleacetaldehyde
Aldehyde dehydrogenase
5-hydroxyindoleacetic acid (5-HIAA)
Excreted in urine

Carcinoid Crisis

- Extreme changes in blood presure
- Confusion/stupor
- Profound flushing
- Diarrhoea
- Bronchospasm
- Hyperthermia
- Cardiac arrythmias

Treatment

- Somatostatin – very short acting
- Analogues are longer acting – octreotide
- Give additional dose prior to surgery to prevent carcinoid crisis

- Long term S/E
  - Billiary stones/sludge
  - Steatorrhoea
  - Reduced glucose tolerance

Modalities for diagnosis

- Endoscope
- CT
- MRI
- Somatostatin receptor imaging, Octreoscan

Non-surgical therapies

- Radio-frequency ablation
- Hepatic artery embolisation and chemoembolisation
- Hepatic radioembolisation

Medical therapy

- Somatostatin Analogues SSAs
  - Controls release of hormones
  - Inhibits growth
- Interferon alpha
  - Antiproliferative
  - Side effects preclude use: flu-like, anorexia, fatigue, myelosuppression, hepatotoxicity
- Everolimus
  - Cell growth, proliferation and apoptosis
  - s/e myelosuppression, diarrhoea, stomatitis, hyperglycaemia.

- Sunitinib
  - Anti-angiogenic
  - s/e hypertension, myelosuppresion, palmar-plantar erethrodysesthesia
- Peptide receptor radionucleotide radiotherapy
  - s/e myelodysplasia and renal
- Cytotoxic chemotherapy
  - Alkylating agents
    - Streptozocin and 5-FU
    - Temozolomide and thalidomine/bevacizumab

References

- https://www.frontiersin.org/files/Articles/704639/fneur-12-704639-HTML/image_m/fneur-12-704639-g002.jpg
- https://media.springernature.com/lw685/springer-static/image/art%3A10.1038%2Fnrdp.2016.35/MediaObjects/41572_2016_Article_BFnrdp201635_Fig1_HTML.jpg
- https://els-jbs-prod-cdn.jbs.elsevierhealth.com/cms/attachment/db26693b-ec2f-4ffc-9eca-37fa99f4b29c/gr1_lrg.jpg
- https://www.researchgate.net/profile/Pornchai-Leelasinjaroen/publication/267044520/figure/fig2/AS:731016918491136@1551299423471/Endoscopic-ultrasound-guided-fine-needle-tattooing-image-of-a-155-mm-hypoechoic-mass.png3
- Rahm Makan & Cloete Van Vuuren (2020): Necrotising migratory erythema leading to the diagnosis of a metastatic glucagonoma without diabetes, Journal of Endocrinology, Metabolism and Diabetes of South Africa, DOI: 10.1080/16089677.2020.1793487
- https://cdn.sanity.io/images/ovv8moc6/patientcare/f37ee0ec7054d864aff7ead1acd4d797c9a4bf8d-409x452.png
- Jensen RT. Natural history of digestive endocrine tumors. In: Mignon MCJ, editor. Recent advances in pathophysiology and management of inflammatory bowel diseases and digestive endocrine tumors. Paris, France: John Libbey Eurotext Publishing; 1999. p 192–219.
- Gullo L, Migliori M, Falconi M, et al. Nonfunctioning pancreatic endocrine tumors: a multicenter clinical study. Am J Gastroenterol 2003;98:2435–9
- Sleisenger and Fordtran. Gastrointestinal and liver disease