INSULINOMA

Incidence: 1/1000000/yr Prevalence: Age: Gender: 60-75% female

PATHOLOGY

90% sporadic (10% MEN1) ||90% benign

Site: Solitary (unless MEN1); uniformly throughout pancreas

Usually <2cm

Insulinoma and MEN1:

10% of insulinomas occur in MEN1 (90% are sporadic); 20% of MEN1 develop insulinoma

Multiples in MEN1

Body/tail: distal pancreatectomy/subtotal +/- splenectomy as almost always have other tumours

Head: enucleation or pancreatico-duodenectomy

Multiple NFpNETs confuse localisation of hypersecreting tumour →Calcium angiography finds active tumour

SYMPTOMS AND SIGNS

1. **Hypoglycaemic episodes:** Neuroglycopenia (anxiety/dizziness/obtundation/confusion/unconsciousness/seizures/ personality change) *commonly in early morning when glycogen stores low
2. **Weight gain (80%): attempt to treat symptoms with increased caloric intake (**often found during attempted wt loss)

BIOCHEMICAL DIAGNOSIS

(a)Whipple's triad: symptoms of hypoglycaemia, CBG <3mmol/l, relief of symptoms after glucose administration

(b)Plasma insulin >5uU/ml + hypoglycaemia + symptoms is most diagnostic (usually exceeds 10)

*Factitious hypoglycaemia excluded: **c-peptide** (exog. insulin) || **urinary sulphonylurea** concentrations (oral hypoglycaemics)*

Pro-insulin >25%

C-peptide >1.7ng/mL (bio-inactive by-product of enzymatic insulin cleavage from proinsulin)

PLC/PLC:total IRI/C-Peptide up in insulinoma/normal in factitious hypogly. (13-22% insulinomas don't secrete c-peptide or PLC)

Cannot discriminate between sporadic and MEN1 insulinoma on biochemical parameters

Supervised standard fasting test:

Baseline examination (memory, calculations, coordination)

Patient drinks non-caloric beverages for 72 hours and measure SBG + immunoreactive insulin conc

Neuroglycopenic symptoms appear: immediate measurement of SBG, serum insulin, c-peptide, pro-insulin concentrations

Neuroglycopenic symptoms appear within 24 hours in 60% of patients

TUMOUR LOCALISATION

After biochemical diagnosis → localise tumour/exclude metastases ie feasibility and extent of resection

1. **CT Pancreatic protocol** 40-80% sensitivity for insulinoma
2. **MRI (T2)** - similar sensitivity to CT

Both detect tumours 1cm+ in pancreas; 4cm+ is likely to be malignant insulinoma (rare)

3. **EUS:** tumours too small for CT/MRI ie 2mm+; more sensitive than CT/MRI (94%)

Detection highest in head, lowest in body and tail (can only view via stomach but 3 angles for head)

4.Calcium arteriography used in negative CT/MRI/EUS; sensitivity 94% with few false positive:

-selective cath of GDA and SMA; calcium gluconate injected sequentially; measure RHV insulin; x2= territory localised

5. If still occult: **manual inspection and IOUS at laparotomy** identifies 90%

OPERATIVE MANAGEMENT

Open exploration of unlocalised tumour

Virtually all insulinomas confined to gland/solitary/uniform distribution (unlike gastrinoma)

IOUS is best intra-operative method to identify insulinoma (sensitivity approaches 100%)

Laparoscopic surgery:

Useful for enucleation of the typically small, benign tumours ||Can proceed to formal resection

Cannot palpate tumour so IOUS mandatory

Resection:

(A)*Enucleation* is the operation of choice

(B)*Resection* (spleen-pres. distal pancreatectomy /subtotal pancreatectomy for tail|| pancreatico-duodenectomy for head if:

1. Cannot separate tumour from pancreatic duct/major vessels (IOUS)
2. Large
3. Evidence of malignancy (locoregional node involvement or invasion)

Frozen-section traditionally used as endpoint of surgery (confirmation of pNET)

MEDICAL MANAGEMENT

Ineffective; only if 1.unlocalisable 2. unresectible malig with mets

Aims:

1. *Prevent hypoglycaemia:* Euglycaemia maintained by frequent high-carb feeds
2. *Reduce insulin release* Diazoxide inhibits insulin release in 50% (weight gain, hirsutism, oedema in 50%)

*stop 1 week before surgery as contributes to intra-operative hypotension

**Octreotide is unpredictable in inhibiting insulin release →not recommended*

OUTCOMES

Cure rate >95% with normal long-term survival

Malignant insulinoma with mets: 30% resectable; median survival unresected 11mths; tumour debulking can -> 4 yr survival

GASTRINOMA

Age: Gender: Incidence: 3/1000000/year Prevalence: second commonest functional pNET

PATHOLOGY:

a- cell tumour
Excessive gastrin secretion → (i) **acid hypersecretion** complications (ii)**secretory diarrhoea**
90% malignant; 10% benign
Mortality from primary and mets, not acid hypersecretion/diarrhoea

Gastrinoma triangle: neck and body of pancreas||junction of CBD/CD||D2/3||*contains 80% of primary gastrinomas*
a)**Most in prox duodenum**; less frequent with distal progression (D1 56%, D2 32%, D3 6%, D4 6%)
b)**Pancreas**: tail 48%, head 30%, body 22%
Ectopic sites: ovary, jejeunum, omentum
Nodes: peripancreatic/coeliac/hilar (can also arise as primary in a single node!)
Metastasize: liver and bone

SYMPTOMS & SIGNS

1. Epigastric pain/oesophagitis symptoms
2. Diarrhoea (gastrin-induced hypersecretion and increased bowel motility)
3. Necrolytic migratory erythema

Most frequently present with solitary DU (similar to non-ZES PUD) so typical ulcer patterns don't exclude ZES
Suspect: All operated for PUD/recurrent ulcers/unusual locations/multiple ulcers/no *H. pylori*/chronic diarrhoea

BOICHEMICAL DIAGNOSIS OF ZES:

1.Serum gastrin > 100pg/mL (Normal fasting serum gastrin excludes ZES; antacids/PPIs lead to false-positives)
2. BAO (basal acid output) >15 mEq/hr (Excludes achlorhydria as a cause for elevated gastrin)
*If only moderate gastrin elevation, **Secretin** provocation testing done after overnight fast*

MEDICAL MANAGEMENT:

Control acid hypersecretion (2-5x PPI dose keeps BAO<15): resolves ulcers in virtually all patients

PRE-OPERATIVE LOCALISATION

1. Somatostatin Receptor Scintigraphy (SRS): 80% of gastrinomas.
2. CT: sensitivity (50%)
3. MRI(T2): low sensitivity for primary; excellent for metastases
4. EUS: 94% sensitive for pancreatic gastrinoma peripancreatic LN mets; poor sensitivity for duodenal gastrinoma (50%) disappointing as the majority are here

SURGICAL MANAGEMENT:

Mortality from primary and mets, not acid hypersecretion → goal of treatment = radical resection
1. Aggressive resection →prevention invasion and metastatic spread (cause of mortality)
2. Allows omission of acid-suppressive med when gastrin normalised (acid not cause of mortality)
3. Gastrinoma associated with development of gastric carcinoid (Type 2)

MEN1:
Parathyroidectomy first: normalisation of calcium will decrease serum gastrin
Resecting gastrinoma in MEN1 does not necessarily cure ZES
70% in MEN1 are duodenal; 50% have multiple duodenal tumours
16% disease free post-op/6% disease free at 5 years so only explore to reduce risk of liver spread

1. DUODENOTOMY:
IOUS poor at detecting duodenal gastrinomas (sub 6mm) + difficult to palpate → duodenotomy mandatory in ZES

2. PANCREATIC RESECTION:
Enucleation is method of choice: non-invasive, small, away from duct and vessels
Larger tumours/near vital structures/locally aggressive mandate pancreatic resection

OUTCOMES

Improved survival with surgery in both **sporadics of all sizes** and **MEN1/ZES if tumour >2.5cm**
Sporadics: 40% disease free at 5 years
MEN1: 6% disease free at 5 years
Liver mets at time of presentation have 38% survival overall

RARE pNETS AND MALIGNANT pNET MANAGEMENT

VIPoma
Glucagonoma
Somatostatinoma
ACTHoma
PTHoma
Neurotensinoma
Calcitonin-secreting pNET
GRF-oma

All similar to gastrinoma: high tendency to be malignant (pNETS are malignant in 60% overall)
Each can arise in MEN1
Pre-operative CT necessary to localise tumour and hepatic mets/LN mets
Only curative treatment is aggressive surgical resection
Palliative resection for locally advanced tumours: reduce symptoms and prolong survival
Resection of liver mets improves 5 year survival
Extensive bi-lobar liver mets preclude surgery (treat with IFN-a or octreotide) but surgical resection can increase 5 years survival to 73%
Octreotide unpredictable; IFN-a addition may help in controlling symptoms from extensive mets if added to octreotide

NON-FUNCTIONAL pNETS

2/100000/year incidence
May still produce hormones (gastrin, insulin, somatostain etc)
May stain for insulin, gastrin or somatostatin on immunohistochemistry so cannot differentiate from functionals
Stain for Chromogranin A: monitor disease progression/relapse/treatment response; also stain for synaptophysin
70% malignant; 60% liver mets at diagnosis
Symptoms: mass effect or other vague symptoms
Surgical resection mandatory so must differentiate from pancreatic adenocarcinoma by SRS
Enucleation advocated even for small NFpNETS as these can metastasize to LNs/liver and histological differentiation correlates poorly with prognosis