HYPERPARATHYROIDISM

1° Dysfunction of gland raises plasma calcium set point
2° Prolonged hypocalcaemia → parathyroid hyperplasia
3° Longstanding secondary HPT → autonomous gland function

PRIMARY HYPERPARATHYROIDISM

Age: 30-50 Gender: Female (3x) Incidence: increases with age (DEXA screening) Prevalence: 3/1000
Risk factors: head & neck irradiation
Part of MEN I/IIa

PATHOLOGY (3 entities: adenoma, hyperplasia, carcinoma)

SINGLE ADENOMA (90%)
-MEN1/RET MEN2A/PRAD1 sporadic/CDC73 hPT jaw-tumour syndrome; usually monoclonal
-Macro: large tan/beefy red with other glands atrophic/normal
-Micro: solid sheets of chief/oxyphil cells in fibrous capsule + rim of normal PT tissue; less stromal fat loss

DOUBLE ADENOMA(5%); if on one side, explore the other

MULTIPLE GLAND HYPERPLASIA (5%)
-polyclonal expansion of parathyroid cells (mainly familial ie MEN1/2A, can be sporadic)
-Macro: not uniform (false impression of single-gland disease)
-Micro: chief cells; more fat loss than single adenoma

CARCINOMA (<1%)
-Younger than HPT with ESI and 5 year survival 69% (death due to hypercalcaemia)
-Macro: features of invasion eg RLN palsy
-Micro: atypia/mitotic figures/capsular invasion

Frozen section: imprecise histo differentiation between pathology; only useful to weigh glands
Size + weight most important determinants of abnormality (threshold= 75mg)

FEATURES

Symptomatic or asymptomatic presentations

(a)Hypercalcaemia: Fatigue (80%), GI features etc
(b)High PTH:
Renal: calculi (oxalate and phosphate), nephrocalcinosis
Bone: osteitis fibrosis cystica (brown tumours, pepperpot skull), osteodystrophy (met. acid.), o'malacia, o'porosis
Soft tissue: chondrocalcinosis, proximal myopathy and hypotonia

Biochemical features:
Renal: calcium reabsorption, loss of phosphate, sodium and bicarb → metabolic acidosis
1aOHase activity → Vit D → increased gut absorption of Ca^{2+} and Pi/renal reabsorption of Ca^{2+}/bone reabsorption
Bone: resorption and formation (raised ALP)

DIAGNOSIS (diagnosis is biochemical)

Plasma calcium: raised (can be decreased if Vit D deficiency/hypoalbuminaemia) so check ionised calcium
Plasma PTH: raised
Plasma phosphate: reduced (unless renal impairment ie secondary/tertiary HPT)
Metabolic acidosis (bicarb excretion)
Chloride: phosphate ratio: 33+ implies HPT in both normal/hypercalcaemic patients
ALP raised (bone turnover)
24 hour urine: hypercalciuria excludes benign familial hypercalcaemic hypocalciuria
AD disorder of renal Ca2+-sensing receptor mimics pHPT: hyperCa2+, hypocalciuria, Ca2+:Cr clearance ratio <0.01
DEXA (for all): decreased bone density, ground glass skull, loss of foramina dura around teeth, OFC features
ECG: features of hypercalcaemia (long PR, short QT, depressed T waves)
If PTH and Ca are very high, consider carcinoma

MANAGEMENT

PRIMARILY SURGICAL AS MEDICAL INTERVENTIONS DON'T ADDRESS UNDERLYING PATHOLOGY
(**a)SYMPTOMATIC PHP** - parathyroidectomy
(b)ASYMPTOMATIC PHP – *still derive benefit in QoL from operation (AAES 2016)*
-Development of symptoms
-Serum calcium >0.25mmol/L above upper limit
-Decreased renal filtration/creatinine clearance (<60ml/min)
-Osteoporosis (BMD T-score <-2.5 or any fragility fracture esp hip, radius, vertebra)
-Nephrolithiasis/nephrocalcinosis
-Age <50
-Patients requesting surgery
-Patients unsuitable for long-term surveillance

Surgery: decreases long-term risks of hypercalcaemia on bone health and nephrolithiasis/calcinosis
Radiotherapy: not indicated except for palliative management of carcinoma
Medical: temp in acute hypercalcaemic crises/mild disease with low risk of long-term sequelae/poor op candidates

HYPERCALCAEMIC CRISIS

Definition: severe hypercalcaemia + acute symptoms
Features: dehydration and thirst, impaired concentration and memory loss, nausea and vomiting, muscle weakness and bone pain
Investigations: (i)PTH to differentiate 1o vs malignancy THEN (ii)US+sestamibi *beware PT cancer v high Ca2+ *
Management:

rehydrate (UO 100ml/hr), diuresis (loop → calciuresis), pre-op workup for theatre (parathyroidectomy)
Intra-op: IOPTH (PTH t1/2 2-3mins so measure up to 30mins to find 50%+ drop in PTH)
post-op: PTH 1 hour post-op cheaper than IOPTH; Ca2+ morning after then 6wks, 6mths (persistent), 12mths (recurrent HPT)

Bisphosphphonates only in malignancy hypercalcaemia, not in PHPT as inhibit osteoclasts so get hypocalcaemia after PTx

Other: salmon calcitonin, steroids, dialysis

IMAGING AND LOCALISATION

ULTRASOUND: limitations so combined with thyroid scintigraphy to:
(i)identify intrathyroidal adenomas (ii)distinction from thyroid nodules(iii)define depth/number of adenomas
(iv) FNA to increase sensitivity (detect PTH; cytology cannot differentiate between PT and Thy tissue)
Sensitivity 80%, specificity 80%, reoperative sensitivity 40%, false positives 20%
Good: no radiation, can assess morphology, FNA
Bad: poor in (a) deep/posterior areas (retrooes/trach/stern and mediast) (b)lesions <5mm, operator dependent, less sensitive for reoperative cases

CT WITH CONTRAST
Sensitivity 80%; Specificity 80% with 50% false positives
Good: accurate, anatomical info, differentiate from thyroid nodules, can combine with FNA, weight estimation
Bad: previous surgery causes artefact, radiation, contrast

MRI: if scintigraphy fails to localise glands in re-operative PHP cases
Sensitivity 88%; Specificity 95; re-operative sensitivity 88%, false positives 18%
Good: non-contrast, no radiation, no artefact, useful for ectopic adenomas
Bad: (a) can't image normals/glands<5mm/ superior glands(deep to thyroid), (b)cannot combine w/ FNA

SESTAMIBI (Technetium-99m)
Avid uptake into mitochondria of hyperfunctioning PT more intensely than thyroid/slower washout
Differential creates images to localise parathyroid adenomas
3 protocols: 1. Single-isotope dual-phase scan 2. Dual-isotope subtraction scan 3. SPECT analysis
Sensitivity 100%; Specificity 90%; false negatives
Good: excellent accuracy (specific enough to allow unilateral exploration), anatomical localisation, low radiation
Bad: false-negatives with small glands, false +ive with thyroid adenomas, fail to recognise multiple-gland hyperplasia

Tl-^{99m}Tc SCAN (Thallium-201-technetium-99m pertechnetate)
Thyroid and parathyroid take up thallium (especially hyperfunctioning glands); only thyroid takes up technetium
Sensitivity 75%; Specificity 82%; reoperative sensitivity 50%; false positives 25%
Good: low radiation
Bad: poor anatomical detail, least sensitive modality (thus is second line modality)

ANGIOGRAPHY: used for localisation in re-operative cases
Thyrocervical trunks, internal mammaries, carotids, superior thyroid arteries; visualises glands over 4mm
Sensitivity in re-operative cases 60%
Good: visualises multiple adenomas/four-gland disease (Sestamibi can't)
Bad: contrast nephropathy, neurological complications, embolisation

SELECTIVE VENOUS SAMPLING: combined with angio to give 95% sensitivity
Twofold drop in PTH between sample and serum PTH levels
Sensitivity 80% (95% with angiography)
Good: will detect multiple adenomas/four-gland hyperplasia/ectopic glands
Bad: false positive 18% without concomitant angiography

AAES 2016: recommends US combined with sestamibi in first instance
NIH 1990: no localisation; experienced surgeon +bilateral exploration cures PHP in 95%; only for re-op cases

PARATHYROIDECTOMY FOR PRIMARY HYPERPARATHYROIDISM

SOLITARY ADENOMA (commonest scenario)
One gland enlarged and others normal →Excise adenoma and preserve the others
if minimally-invasive approach for single gland, use IPM to ensure not missing MGD

SPORADIC MULTIGLANDULAR DISEASE
Two glands enlarged and two normal is double-adenoma but could be MGD →Excise both adenomas
Three glands enlarged suggests MGD → Excise three glands and preserve fourth
Four glands enlarged is MGD→ Excise three glands and reduce fourth to leave 40-60mg (similar size to normal gland)
Leave gland furthest from RLN to reduce re-operative morbidity (start dissection with this gland)

FAMILIAL HYPERPARATHYROIDISM
MEN1
3 principles: obtain+maintain normocalcaemia for longest time possible/facilitate re-operation/avoid hypocalcaemia
3 options: subtotal w/60mg left, total parathyroidectomy + autotransplantation, total parathyroidectomy
Must always search for ectopic/supranumerary glands (thymectomy + central neck fat resection)
Cryopreservation → autotransplantation if persistent hypoPTH
AAES 2016 recommend SPTx*

Outcome:
Underlying disease predisposes to persistent/recurrent disease
TPT = higher initial "cure" rate than STPT but higher hypoparathyroidism risk

MEN2A
-Less aggressive HPT than MEN1
-Main risk of surgery is hypoparathyroidism - can be worse than mild hyperparathyroidism
-Must rule out phaeochromocytoma before operating
-MGD; often not all glands are enlarged →only excise macroscopically enlarged glands *(AAES 2016 recommendation)*
-Superior glands preserved in preference to inferiors (inferiors necrose in MTC thyroidectomy)
-Inferior gland autotransplantation

PARATHYROID CARCINOMA
If diagnosis confirmed pre-operatively (v high PTH + palpable mass) (grey,enlarged, hard, thick capsule, adherent)
-en bloc excision: tumour +adjacent thyroid lobe+ipsilateral PT+nodes (recurrent, jugulocarotid, pretracheal)
-routinely explore contralateral glands
*prophylactic central or lateral neck dissection not indicated (AAES 2016)
* Frozen section cannot conclusively confirm diagnosis*
* *If diagnosis made post-operatively (paraffin section histology), re-operate to complete as for en bloc resection*
Follow-up: For life, death due to hypercalcaemia →clinical evaluation and serum calcium levels
Outcome: Local recurrences in 50%/distant mets in 30%/5 year survival 86%; 10 year survival 49% for all patients

OVERALL OUTCOME AFTER PARATHYROIDECTOMY
Normocalcaemia: 24-48 hours 95-98% with expert surgeon (less so in MGD than solitaries)
20% MEN1 still hypercalcaemic immediately post-op
Significant hypocalcaemia uncommon (few severe bone involvement; give oral calcium and Vit D)

PTH undetectable 4 hours after surgery; normalise on day 1; elevated 30d post-op in 30%; permanent hypoPTH 1%
Can be adaptive to Vit D deficiency or renal dysfunction or even decreased peripheral sensitivity to PTH

Other: RLN 1% - reinnervate if recognise intra-op; improves vocal strength and aspiration risk(AAES) **Haematoma 1%**
Should have 95%+ cure rate in sporadic pHPT (normalise PTH in hyper/normoca2+)(Normal Ca2+ for 6 mths)
Different endpoint in MEN

PERSISTENT/RECURRENT PRIMARY HYPERPARATHYROIDISM

Persistent HPT: persistent hypercalcaemia due to HPT in 6 months following parathyroidectomy
Causes: (a) negative exploration (b)inappropriate excision (c)carcinoma

Recurrent HPT: reappearance of hypercalcaemia after 6 months of normocalcaemia
Cause: (a)Familial;MGD(b)second adenoma in normal gland (c)CIS (d)parathormatosis (c+d=rupture and local spread)
(e)Graft: autonomy/local stimulating factors/hyperfunctioning if adenoma implanted in forearm

Diagnosis
Start fresh: PTH and ca^{2+}/exclude other causes of hyperca^{2+}(esp BFHH) /look for 2^0 HPT/look for MEN1/2A
Localisation: US and sestamibi routine; CT/MRI if fail OR suspect ectopic; SVS/angio only if these inconclusive
ideal: convergence of results of two modalities for topgraphic certainy, will do in 95%

Graft recurrence
-must be proven before-reoperation (US/sestamibi) (Casanova test: induce ischaemia, test PTH)
-must exclude cervical/mediastinal tissue (ectopic/supranumerary)

Re-operative approach
Solitary adenoma: focused open approach; ioPTH may be helpful
Familial: complete exploration of all residual tissue
MGD: complete exploration of all residual tissue (revision of transverse cervicotomy)
Three normal glands: a previously occult adenoma; guided by localisation studies
PIII identified:
Four normal neck glands, expert surgeon: localisation studies, suspect mediastinum
Cancer/atypical adenoma suspected: suspect local recurrence, look for mets
Several normal glands removed: cryopreservation and later autotransplantation

(a)Posterolateral approach: adenoma in posterocervical site (probably P IV)
-enlarge previous transverse incision laterally on SCM border and dissect behind thyroid
(b)Thyrothymic approach: adenoma visualised anteriorly (probably P III)
-along previous incision, divide infrahyoid muscles as low as possible to access thyrothymic ligaments
(c)Mediastinal approaches
posterior or if anterior above aortic arch: can access from neck
deep anterior or middle mediastinum – anterior mediastinotomy/left thoracoscopy may be preferable to partial or total sternotomy (aided by localisation studies)

Not all patients need re-operation
Must assess vocal cords prior; higher risk of RLN injury
ioPTH and crypopreservation recommended

Autotransplantation debatable: hyperfunctional grafts interfere with assessment of outcome
-cryopreservation; decision for secondary autotransplantation delayed for a year as hypocalcaemia may resolve by then

Outcomes of re-operation
Can hit 95% cure rate; recurrence with hyperfunctional transplanted tissue up to 17%
Morbidity overall 20% (RLN injury 10%, permanent hypoPT in 20%)
Graft failure in up to 50%, moreso with cryopreserved tissue

SECONDARY HYPERPARATHYROIDISM

2º = Prolonged hypocalcaemia → parathyroid hyperplasia (factors other than PT disease →overproduction of PTH)
O'porosis, ricket's, o'malacia, hypermagnaesaemia, lithium, ectopic PTH (eg oat cell Ca), hypophosphataemia, CRF

Renal failure:

1. **Hypocalcaemia/hyperphosphataemia**
stimulates PTH secretion to normalise levels ; Pi progressively retained, Ca2+ even lower→stimulates PTH even *more*
2. Decreased 1a-hydroxylation of 25-OH Vit D
-reduced renal synthetic function + high phosphate→ reduced Vit D3
-calcium acquisition from gut, kidneys and bone reduced → PTH goes up
3. Bony resistance to PTH
4. Change in PTH set point (serum calcium that drops PTH by 50%): inhibition of PTH secretion lost → SHP
5. Aluminium intox: in renal dialysate/Pi binders →accumulates in bone→o'malacia→exacerbates PTH production

FEATURES

BONE PAIN/FRACTURES: (a) OFC → woven bone →remodelling/compression fractures (b)PPskull/brown's tumours
PRURITIS: 85% of patients on haemodialysis, relief by parathyroidectomy
METASTATIC CALCIFICATION: any system; esp vasculature/PTx decreases severity everywhere except vasculature
CALCIPHYLAXIS: soft tissue +vascular calcification → tissue necrosis (mottled violaceous lesions → ulcers/gangrene)
-Commonest in extremities but can be anywhere/50% mortality/high calciumXphosphate product
-Treat with phosphate binders and parathyroidectomy

TREATMENT

(a) INITIALLY MEDICAL – bring serum Ca2+/Pi to physiological levels →remove impetus for PTH overproduction
Supplements: Calcium (1500mg/day), Vit D
Binders: Phosphate/Aluminium (desferroxamine)
Haemodialysis with calcium-enriched dialysate
Phosphate-poor diet (<1000mg/day)
Cinacalcet: calcimimetic binds to calcium-sensing receptor to drop PTH secretion

(b)DEFINITIVE – renal transplant (but can get tertiary HPT)

(c) PARATHYROIDECTOMY (4-gland with autotransplantation or 3.5 gland removal)
-indicated in 5-10% who fail medical therapy (uncontrollable hypercalcaemia)(high PTH)
-for management of above 4 features

SURGICAL MANAGEMENT

Underlying disease predisposes to persistence/recurrent → palliative intent (same 3 principles as MEN1)
Localisation unnecessary: all undergo bilateral neck exploration
Must detect supranumerary/ectopic glands (higher incidence due to hyperstimulation)

Strategies:

1. SPTX (less hypoCa2+, higher recurrence, higher morbidity at reop.): kids/transplant intended/normal PT tissue
2. TPT+AT (more hypoCa2+, less recurrence, lower morbidity at reop.): MGD/not for transplant
3. TPT-AT (permanent hypocalcaemia , less recurrence/persistence): need Vit D and oral calcium for life
Central neck fat resection and thymectomy to supranumerary glands
Cryopreservation: necrosis of remnant →permanent hypoPT; leave for 6 months then decide

Persistence/recurrence (2-12%)

(1)Surgical: incomplete removal/remnant left is too large (>60mg)
(2)Graft hyperplasia/autonomy
(3)Supranumerary glands: 15% dialysis pts have neck/mediastinal supranumeraries; hyperstim → gain function
(4) Ectopic glands
**ALL undergo localisation studies (must look for supernumerary glands in neck and mediastinum)
**Casanova test

TERTIARY HYPERPARATHYROIDISM

Chronic renal failure with resolution of renal disease (eg transplant) but had developed autonomous glands

Once freed from metabolic disarray, glands continue to pump out PTH without negative feedback inhibition

-impaired renal graft function
-insufficient calcitriol conversion by kidney
-autonomy or slow involution of glands
-non-suppressible PTH secretion

60% TPT resolve spontaneously (50% normalise hypercalcaemia in first month, 95% in 6 months)
If after 12 months' observation, still a problem → parathyroidectomy
70% abnormal bone biopsy and elevated PTH persistence
Only 0.2-0.3% of renal transplant patients require parathyroid surgery
Indications: (a)severe hypercalcaemia (>3) (b)symptomatic hypercalcaemia for 2+ years

Transient hypoPTH of surgery can impair graft perfusion, consider SPTX
Recurrence is rare

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The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism

http://jamanetwork.com/journals/jamasurgery/fullarticle/2542667