TOPICS:
(1) Gynaecomastia
(2) Galactorrhoea
(3) Hirsutism

DR TANJA KEMP
ENDOCRINOLOGY AND METABOLISM UNIT
STEVE BIKO ACADEMIC HOSPITAL

(1) GYNAECOMASTIA
Case presentation

- Mr. IT, a 40 year old man from Eersterust

Social history:
- Married, security worker
- Ex-alcohol binger (no alcohol for 5 years)
- Smoker: 20 pack years
- No recreational drugs or cannabis

Referral to SBAH for:
  → Gynaecomastia

Medical history:
- Gynaecomastia started 2 - 3 years ago
- Non-tender breasts
- Asymmetrical (left larger than right)
- No galactorrhoea
- Erectile dysfunction x 2 years with decreased morning erections as well
- Decreased libido
- Decreased shaving
- One child, 11 years of age; wife off contraceptives x 6 years, has not fallen pregnant yet
Medical history (cont):
- No marital problems
- Stress at work
- Past peptic ulcer disease: uses Ranitidine chronically and Metoclopramide on and off
- Did have mumps as a teenager
- No other chronic medical problems / medications

Examination:
- Clear gynaecomastia (C-cup); left larger than right; not tender; no breast nodules/masses
- L testis = 10ml, R testis = 12ml (slightly small); no masses palpable
- Signs of hypogonadism (decreased body hair)
- No signs of chronic liver disease or of thyrotoxicosis
- No features of Klinefelters’ syndrome
- No anosmia (Kallman’s syndrome)
What is gynaecomastia?

- Benign proliferation of the glandular tissue of the male breast
- Clinically: presence of a rubbery or firm mass extending concentrically from the nipple(s)
- Can be unilateral or bilateral
- Caused by an increase in the ratio of oestrogen to androgen activity

Who develops it?

- Common in: - infancy (60-90%)
  - adolescence (up to 65%)
  - middle-aged to older adult males
- Pseudogynaecomastia
  - is often seen in obese men ("moobs")
  - fat deposition without glandular proliferation
  - doesn’t require evaluation
Causes?

- **Physiologic** gynaecomastia
  - infants
  - adolescents
- **Pathologic**
- **Idiopathic**
Puberty

- Transient increase in oestradiol concentration at the onset of puberty
- The serum oestradiol concentrations rise to adult levels before the testosterone concentration
- Thus: transient imbalance of oestrogen and androgen
- Usually resolves spontaneously within 6m – 2 years of onset, but may persist

Adults

- Persistent pubertal gynaecomastia (25%)
- Drugs (10-25%)
- Idiopathic / no detectable abnormality (25%)
- Cirrhosis or malnutrition (8%)
- Hypogonadism – primary (8%); secondary (2%)
- Testicular tumours (3%)
- Hyperthyroidism (1.5%)
- Chronic renal insufficiency (1%)
Drugs

Antiandrogens/inhibitors of androgen synthesis:

- Cyproterone acetate
- Finasteride
- Spironolactone
- Ketoconazole
- Tea tree oil

Antibiotics:

- Ethionamide
- Isoniazid
- Ketoconazole
- Metronidazole
Antiulcer drugs:

- Cimetidine
- Ranitidine
- Omeprazole

Cancer chemotherapeutic drugs:

- Methotrexate
- Vinca alkaloids
- Combination chemotherapy
Cardiovascular drugs:

- ACE-inhibitors: captopril, enalapril
- Amiodarone
- Calcium channel blockers: diltiazem, nifedipine
- Digoxin
- Methyldopa

Drugs of abuse:

- Alcohol
- Amphetamines
- Heroin
- Marijuana
Psychoactive drugs:

- Diazepam
- Haloperidol
- Phenothiazines
- Tricyclic antidepressants

Hormones:

- Androgens
- Anabolic steroids
- Estrogens
- Growth hormone
Other:

- HAART
- Metoclopramide
- Phenytoin
- Theophylline

HIV

HAART:

- = usually due to fat tissue (pseudogynaecomastia) as part of a fat redistribution syndrome (lipodystrophy)
- True gynaecomastia can be caused by hypogonadism
- Oestrogen-like effects of some drugs, especially Efavirenz
- Malnutrition
Cirrhosis or malnutrition

- Prevalence of gynaecomastia in cirrhotic patients as high as 67%
- Starvation / refeeding gynaecomastia

Male hypogonadism

- Primary hypogonadism
  - testicular problem
  - Klinefelter’s syndrome
- Secondary hypogonadism
  - pituitary or hypothalamic problem
  - Kallman’s syndrome
When to investigate?

- Recent onset
- Painful
- Signs or symptoms of hypogonadism
- Adolescents: just observe 6-monthly

How to diagnose?

- A palpable mass of tissue at least 0.5cm in diameter (usually underlying the nipple)
- NB: men can also get breast cancer!
How to investigate?

- **History:** NB – drugs!
  - how sudden was onset / pain / tenderness / associated complaints
- **Physical examination:**
  - pseudogynaecomastia / gynaecomastia / cancer
  - look for symptoms and signs of renal or liver disease / hyperthyroidism / intersex / anosmia / Klinefelter’s syndrome / hypogonadism
  - abdominal mass / testicular mass
**Special investigations:**
- Sonar / mammogram if not sure about gynaecomastia
- Karyotype if signs of Klinefelter’s
- Testosterone (T), LH, oestradiol
- hCG

**Possibilities in our patient:**
- Drugs: - ranitidine
  - metoclopramide
- Past alcohol abuse (possible liver disease)
- Past mumps (possible testicular problems)
Our patient’s results:

- Normal U&E, LFT, TFT, HCG, oestradiol
- Testosterone: 5.11 nmol/l (N = 6.07 – 27.10)
- LH: 2.6 IU/l (N = 1.2 – 8.6)
- FSH: < 1.7 IU/l (N = 1.3 – 19.3)
- Prolactin: 190.9 / 184.8 μg/l (N = 2.5 – 17)
- MRI of pituitary: pituitary not enlarged
  but: ? hypodense lesion ? microadenoma

Diagnosis:

= Hyperprolactinaemia due to a possible pituitary microprolactinoma

How to treat?

Depends on:

- Aetiology
- Duration
- Severity
- Presence or absence of tenderness
Spontaneous regression

- Recent onset (<6m) often regress spontaneously (adults and adolescents)
- Pubertal: regression in 85-90% within 6m – 2yr
- Persistence beyond age 17 is uncommon
- > 12 months: unlikely that medical therapy will cause significant regression in the late fibrotic stage

Treatment

- Observation only
  - initial step for most adolescents, and for most men after treating underlying cause
- Drug therapy
  - early therapy if severe breast enlargement, pain, tenderness, and embarrassment that interferes with daily activities
- Radiotherapy
  - prophylactic before therapy for prostate cancer
- Surgery
  - reduction mammoplasty
  - not before completion of puberty
Drugs

- **Androgens**
  - testosterone (only for hypogonadism)
  - dihydrotestosterone
- **Selective oestrogen receptor modulators**
  - tamoxifen, raloxifene
  - anti-oestrogen effects
  - particularly useful in reducing pain and swelling if gynaecomastia is of recent onset
- **Aromatase inhibitors**
  - anastrazole
  - block oestrogen biosynthesis
  - in trials: not effective

Spontaneous regression:
Post-surgery:
- only small scar

Therapy in our patient:
- Dopamine agonist:
  - Parlodel (Bromocriptine): 2.5mg bd (titrating up)
- Added now Sustanon (Depot Testosterone)
  250mg IMI monthly for severe hypogonadal complaints
- Should be able to stop Testosterone once prolactin normalized
- Will most likely need mastectomies in near future
(2) HYPERPROLACTINAEMIA/GALACTORRHOEA

Case presentation

- Miss PM, a 38 year old female from Mamelodi

Social history:
- Single, clerical work (now unemployed), 1 child
- Alcohol: nil
- Never smoked
- No recreational drugs or cannabis

- Referral to SBAH for:
  → Galactorrhea
Medical history:
- Galactorrhoea started 1 year ago
- Both breasts involved, more than one duct
- Mainly occurs on pressing breasts, but occasionally spotting on bra
- White and yellow fluid present
- Regular menses, but menorrhagia, dysmenorrhoea and short cycles present

Medical history (cont):
- One child, age 21
- Never tried to fall pregnant after that, never used contraceptives (abstained)
- Iron deficiency anaemia, uses iron supplements
- Surgeons already performed a sonar of breasts and a mammogram: all normal
- No other chronic medical problems / medications / the Pill / hormones
Examination:
- Clear galactorrhoea: milky discharge from 3 ducts of the right breast, milky discharge from 1 duct of the left breast, yellow watery discharge from another duct of the left breast
- No masses palpable in the breasts
- No evidence of pregnancy
- No signs of hypothyroidism
- No visual field outfall

What is it?
- **Hyperprolactinaemia** = high serum prolactin
  - common abnormality which usually presents with hypogonadism and / or galactorrhoea
- **Galactorrhoea** = lactation in the absence of breastfeeding
- Most women who have hyperprolactinaemia do not have galactorrhoea
- Many women who have galactorrhoea have normal serum prolactin values
Galactorrhoea

- Milk secretion can continue for at least 6 months after delivery or after cessation of breastfeeding
- Usually bilateral and white or clear
- May be unilateral and a variety of colours including yellow, green, brown, or gray
- Occasionally bloody during pregnancy or lactation
- Prolactin stimulates milk secretion but not breast development (needs oestrogen +- progesterone)
- Galactorrhoea thus rare in men unless also gynaecomastia due to hypogonadism
- DA = dopamine
- PROL = prolactin
- PRF = prolactin releasing factor (none has been identified yet)

Symptoms and signs of ↑ prolactin

- **Postmenopausal women:**
  - asymptomatic (already hypogonadal)
  - occasionally visual field outfall or headaches if large pituitary tumour

- **Premenopausal women:**
  - galactorrhoea
  - hypogonadism: oligomenorrhoea
  - secondary amenorrhoea
  - anovulation with infertility
  - hot flashes
  - vaginal dryness
  = central hypogonadism (inhibition of LH +- FSH)
Symptoms and signs (cont)

- Correlation between level of prolactin elevation, and:
  - symptoms
  - size of tumour if prolactinoma is present

- **Mild** elevation (20 – 50 ng/mL): can cause infertility even when menstruating normal; insufficient progesterone secretion with anovulation; present in 20% of women evaluated for infertility

- **Moderate** elevation (50 – 100 ng/mL): amenorrhoea or oligomenorrhoea

- **Significant** elevation (> 100 ng/mL): overt hypogonadism

Symptoms and signs (cont)

- **Men:**
  - galactorrhoea very rare
  - **hypogonadism**: decreased libido
    - impotence
    - reduced shaving frequency
    - infertility (4% of infertile men)
    - gynaecomastia
    - lethargy, decreased energy
  - **erectile dysfunction** not only due to hypogonadism, but is directly related to high prolactin
  - in long term hypogonadism causes: decreased body hair, osteoporosis, decreased muscle mass
Causes of hyperprolactinaemia?

- Physiological
- Drug-induced
- Pathological

Physiological:

- Stress (e.g. post-seizure)
- Pregnancy
- Lactation
- Nipple stimulation
- Sleep
- Coitus
- Exercise
- Baby crying
Pathological

- disconnection hyperprolactinaemia / “stalk effect”
- prolactinoma (usually microadenoma)
- primary hypothyroidism
- polycystic ovarian syndrome
- macroprolactinaemia
• **Uncommon:**
  - hypothalamic disease
  - renal failure
  - pituitary tumour secreting prolactin and growth hormone

• **Rare:**
  - chest wall reflex (e.g. post-herpes zoster)
  - ectopic source

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**Don’t forget**

• **Macroprolactin**
  - in some people: prolactin becomes bound to an IgG antibody or become glycosylated (="macroprolactin")
  - of no pathological significance

• **Stalk effect / disconnection hyperprolactinaemia**
  - anything that disrupts the inhibitory effect of hypothalamic dopamine on prolactin secretion

• **High dose “hook effect”**: caution in interpreting prolactin concentration between 20 and 200 μg/l in the presence of a macroadenoma
Analytical interference (The Hook Effect)
The huge excess of prolactin (if e.g. >5000 μg/l) saturates both specific and less specific binding sites on both antibodies (capture and signal) preventing “sandwich” formation in the assay.

The Hook Effect
- Result is a prolactin level that is only modestly elevated (falsely lower than it is)
- Avoid this artifact by repeating the assay using a 1:100 dilution of serum
How to investigate?
Clinical examination:

History:
- drugs, pregnancy, breastfeeding, headaches, diplopia, renal / thyroid disease, underwear

Examination:
- Galactorrhoea:
  - type of nipple discharge (how many ducts, colour of fluid, unilateral / bilateral)
  - any masses palpable
- Features of hypogonadism
- Visual field defect
- Chest wall injury
- Signs of hypothyroidism

Red flags with a nipple discharge
- Risk of cancer higher if:
  - spontaneous discharge
  - bloody or positive for occult blood
  - unilateral or uniductal
  - associated with a breast mass
  - women over 40 years
- Benign discharge usually:
  - bilateral
  - multiductal
  - occurs with breast manipulation
Special investigations

- Exclude pregnancy
- Stop offending drugs

**Prolactin:**
- mild elevation (20-40 μg/l): stress, drugs (repeat)
- moderate elevation (20-200): drugs, microprolactinoma, disconnection hyperprolactinaemia
- severe elevation (>200): macroprolactinoma

- Dilution of prolactin; macroprolactin
- TSH, T4, U&E
- CT-scan or MRI of hypothalamus/pituitary

**Complications:**
- LH, FSH, oestradiol or testosterone (hypogonadism)
- DEXA-scan (osteoporosis)
- Eye fields
Our patient’s results:

- Normal U&E, LFT
- Normal TFT, negative β-HCG
- Oestradiol: 381 pmol/l (N = 99 - 1590)
- LH: 7.3 IU/l (N = 1.6 – 12.4)
- FSH: 5.3 IU/l (N = 1.2 – 9.6)
- Prolactin: 16.1 μg/l (N = 3.3 – 26.7 μg/l)

Diagnosis:
= Galactorrhoea without hyperprolactinaemia (idiopathic)
Galactorrhoea without hyperprolactinaemia

- Up to 46% of women with galactorrhoea have a normal serum prolactin (even higher if normal menses)
- Often represents persistent milk secretion following correction of elevated prolactin e.g. after nursing or drug-induced hyperprolactinaemia
- Not the result of ongoing disease, unless blood in fluid (test for occult blood and for fat)

Therapy

- Depends on cause
- Stop offending drugs
- **Dopamine agonist** therapy for hyperprolactinaemia
  - bromocriptine
  - cabergoline
- Troublesome physiological galactorrhoea: dopamine agonists
Therapy in our patient:

- Reassurance
- Dopamine agonist:
  - Parlodel (Bromocriptine):
    - 2.5mg nocte (x 3 months)
    - then: 2.5mg bd if still galactorrhoea
- Gynaecology referral for menstrual problems

(3) A HAIRY PROBLEM
Case presentation

- Mrs ECK, a 65 year old widow, with two children
- Referral from her GP for
  - hirsutism
- Longstanding hirsutism >20 years
- Progressively worse over the last year: now have to shave daily

Medical history

- Possible polycystic ovarian syndrome when young (PCOS)
- Longstanding hypertension; now on 5 drugs
- DM type 2 x 15 years
- Dyslipidaemia
Examination

- BP=130/84
- Pulse=74/min
- BMI=35.6
- Metabolic phenotype; mainly central obesity
- Marked hirsutism and virilization

Hirsutism
Hirsutism

Male pattern baldness
Acanthosis nigricans

Examination

- No clear features of acromegaly
- No clear features of Cushing’s syndrome
- Target organ damage of DM: microalbuminuria, early cataracts
- Rest of examination: normal
- Quantity
- Distribution
- Hair loss

Ferriman-Gallwey Hirsutism Scoring System

J Clin Endocrinol Metab 1961;21:1440
Ferriman-Galwey score

- < 8: not significant hirsutism
- 8 – 15: mild hirsutism
  - only trial of oral contraceptives or cosmetic products
- > 15: moderate hirsutism
  - do a 8h00 serum testosterone
  - check for risk factors for malignancy, polycystic ovarian syndrome, or endocrinopathies

Aetiology

- Drugs
- Familial
- “Hairy diabetic”
- Ovarian causes
- Adrenal causes
- Other endocrine causes
**Special investigations**

- **Total testosterone = 7.3 / 10.3 nmol/l**  
  (within male reference range)
- **LH = 24.6; FSH = 44.9** (post-menopausal values)
- **Oestradiol = 225; SHBG = 33.6** (normal)

**Endocrine causes**

- **Hyperprolactinaemia**
  - prolactin = 9.1 (normal)
- **Thyroid abnormalities**
  - **T4 = 13.9; TSH = 0.81** (normal)
- **Acromegaly**
  - random GH = 0.2 (normal)
  - normal suppression on GTT
Adrenal causes

- **Adrenal tumours (functional)**
  - **Cushing’s syndrome**
    - 8h00 cortisol = 515; 23h00 = 84
    - after Dex-suppression test = 33 (normal)
    - 24h urine cortisol = 389 / 466 (normal)
  - **Adrenocortical carcinoma**
    - DHEAS=1.8 / 1.6 (normal)
    - no adrenal masses seen on sonar
    - no evidence of hypercortisolaemia
    - but: high testosterone

Adrenal causes (cont)

- **Non-classical congenital adrenal hyperplasia / 21 hydroxylase deficiency**
  - 17OH progesterone = 3.2 (normal)
Ovarian causes

- **PCOS**
  - what happens to PCOS in post-menopausal women?

- **Ovarian tumours**
  - sonar: cystic lesion noted in the right ovary;
    fibroid uterus
  - normal Ca-125

Red flags

- The patient’s age
- The rapid progression of hirsutism
- The virilization / degree of hirsutism
- The degree of androgen elevation
- The possible mass seen on sonography
- (Sudden onset)
Final diagnosis

- Total abdominal hysterectomy done, with bilateral salpingo-oophorectomy
- Bilateral hydrosalpinx found
- Benign leiomyomas
- Bilateral stromal hyperplasia of the ovaries on histology
- Post-op testosterone level = 0.4 nmol/l

Treatment of hirsutism

- Treat the cause
- Weight reduction
- Medical treatment of hirsutism
  - oral contraceptives (Diane-35; Yasmin)
  - cyproterone acetate
  - spironolactone
- Insulin-sensitizing drugs
  - Metformin
Treatment