Hypopituitarism – optimising replacement therapies

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Case

History

- 21 year old woman presents with a history of headache and a recent MRI brain scan
  - Migraine with aura for several years
  - Recent dull pressure sensation
  - Visual disturbance
- Regular periods
- Otherwise well
- No medications or allergies
  - Copper IUD for contraception

Examination

- Weight 58.1kg. Height 168cm. BMI 20.6
- BP 106/68
- No clinical signs of Cushing's syndrome or acromegaly
- Not hirsute
- Clinically euthyroid
- Visual fields normal to confrontation
- Eye movements normal

Investigations/Management

Hormone results

- T4 12 pmol/L (ref range 7-17)
- TSH 3.5 mIU/L (ref range 0.3-4.5)
- Cortisol 540 nmol/L at 0730h
- IGF-1 36 nmol/L (ref range 14-46)
- Prolactin 228 mIU/L (ref range 71-566)
- FSH 5.7 U/L
- LH 27 U/L (likely mid cycle peak)
- Oestradiol – wasn't done!

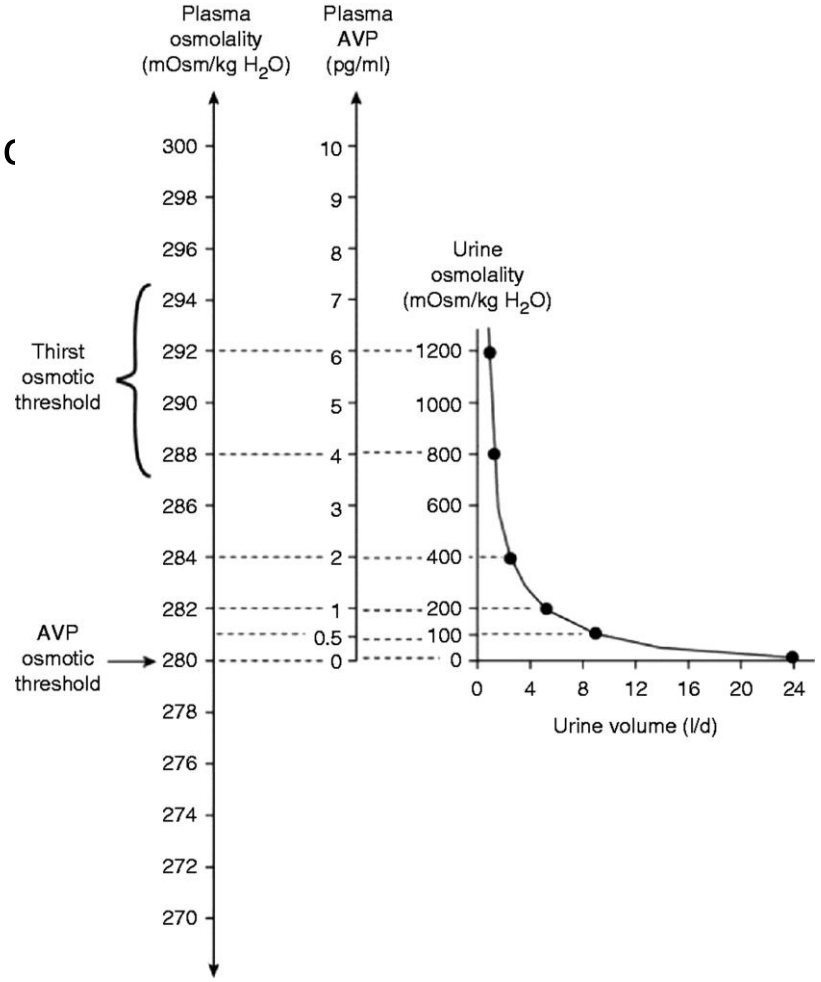
Management

- MRI showed 12 x 13 x 10 mm mass abutting optic nerves and chiasm
- Conservative versus operative management?

- After discussion in multidisciplinary team meeting and with the patient, surgery was decided upon.
- She underwent trans-sphenoidal resection of her pituitary tumour

Post-operative course

- Lumbar drain for csf leak
- She started producing large volumes o operatively
  - Passed 900 ml in an hour
- Associated with thirst
  - Serum osmolality 297 mosmol/kg
  - Urine osmolality 152 mosmol/kg
- Post-operative morning cortisol
  - 30 nmol/L
- Free T4
  - 6.5 pmol/L (ref range 7-17)



Initial management

- She was discharged on…

- Hydrocortisone 10 mg on waking, 10 mg with lunch and 4 mg in the afternoon (24 mg daily)
  - Within the 15-25 mg/day Endocrine Society Guidelines
- Thyroxine 75 μg in the morning
- Desmopressin 100 μg bd

6 week outpatient follow-up

- Patient remains amenorrhoeic
- Fatigue, poor energy
- Weight gain – centrally based
  - 59.4 kg compared to 55.6 kg post-op
- Still thirsty and passing a lot of urine intermittently

Biochemistry results

- Pre-dose cortisol 20 nmol/L
- Free T4 15 pmol/L, TSH <0.05 mU/L
  - on Thyroxine 75 μg daily
- E_2 50 pmol/L, FSH 4 IU/L, LH <2 IU/L
- IGF-1 5 nmol/L (ref range 17-42)

Treatment goals in hypopituitarism

- As close as possible, to normalise target organ hormone concentrations using the administration of exogenous hormones
- To improve and minimise a patient's symptoms of hormone deficiency

Question

- How can this patient's symptoms be addressed?
- Specifically what changes or additions to her current hormone regimen might make her feel better?

Thyroid hormone

- Thyroxine
- Usual dose range 50-150 μg daily
- Adjust aiming for free T4 in mid to upper part of the reference range
- If pre-op tests were normal, one can gauge the individual's free T4 set point
  - Patient's normal free T4 was 12 pmol/L (ref 7-17)
- Low TSH is not a reliable indicator of over-replacement
  - Unlike in primary hypothyroidism

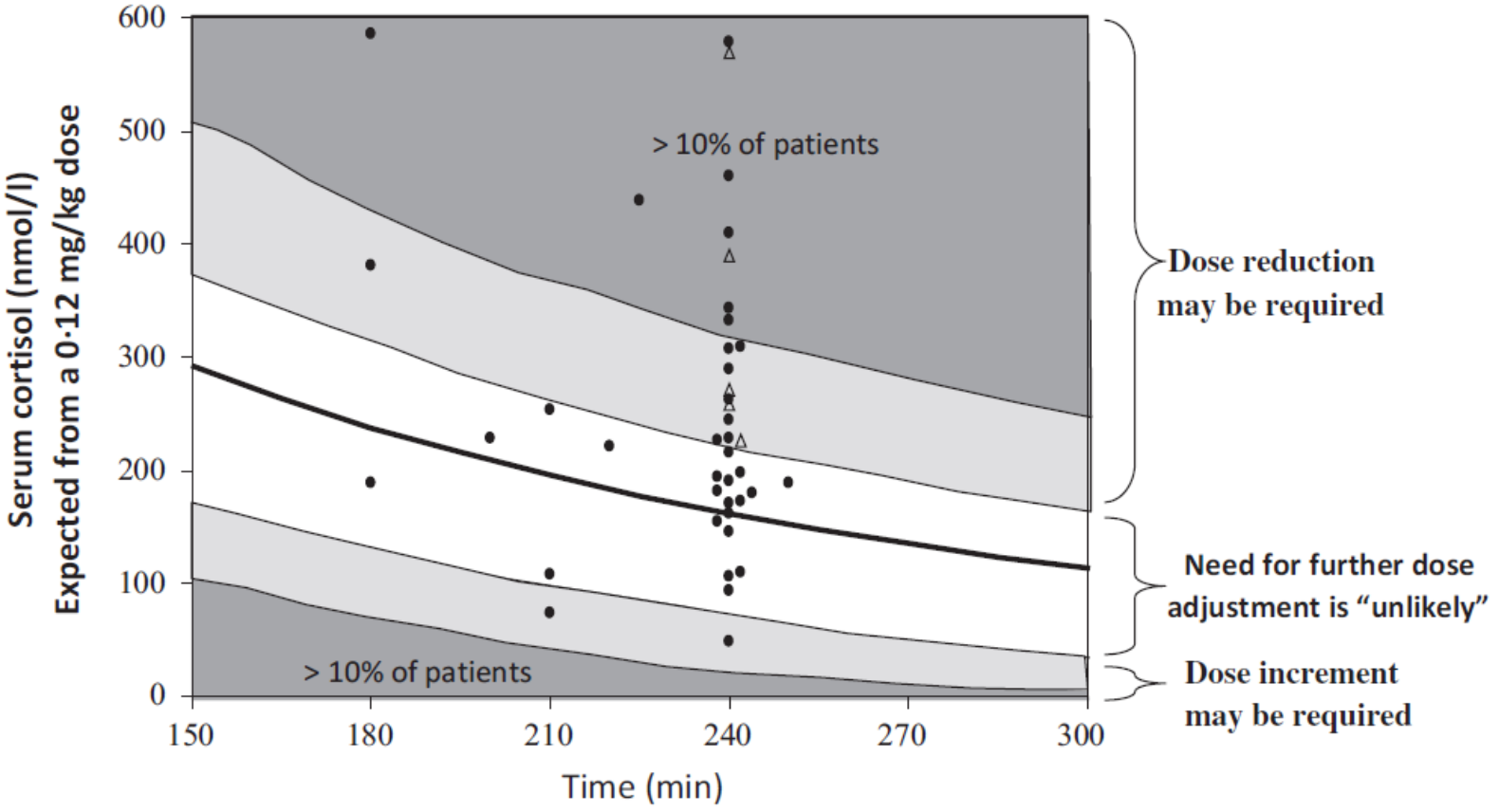
Glucocorticoid replacement

- Hydrocortisone or cortisone acetate
- Usual dose 12-24 mg hydrocortisone or 15-30 mg cortisone acetate daily in 2-3 divided doses

- Hydrocortisone
  - 0.24 mg/kg would be 14 mg/day
  - 10 mg/m^2 would be 16 mg/day

- But large individual variability in absorption and action
- Dose adjustment based on clinical response
  - Serum cortisol monitoring is controversial

4h cortisol level to adjust dose?



Debono and Ross. Clin Endo 2013

Sex steroids

Male

- Testosterone
  - im injection, transdermal gel
- Human chorionic gonadotrophin (hCG)
  - s/c injection 2-3x weekly for fertility induction

Female

- Treat with combined oestrogen + progestin until normal age of menopause
- FSH and hCG injections for ovulation induction

Oestrogen and Progestin replacement for pre-menopausal aged women

- Oral oestrogen antagonises the effect of GH, lowering IGF-1
- Transdermal oestrogen recommended, as no/minimal effect on GH/IGF-1
  - Also no increase in VTE risk.

- Often need 100 μg daily via transdermal route, can monitor E_2 concentrations

- Cyclical progestin results in regular withdrawal bleed
- Continuous combined oestrogen/progestin eliminates period
  - May have breakthrough bleeding
- Mirena IUD provides continuous local progestin to endometrium

Growth hormone

- Well described syndrome of adult GH deficiency
  - ↑ fat mass, ↓muscle mass
  - Decreased quality of life
  - Bone loss, elevated lipids
  - Reduced exercise capacity
- GH treatment for adults not PBS funded in Australia
  - it is in NZ
- ESA/APEG have submitted to PBAC – under review

- Daily sc injection
  - Start at 0.2-0.3 mg/day, up to 0.8 mg/day
- Women need more than men
- Monitor IGF-1, aim for mid normal range.

Diabetes insipidus

- In the context of pituitary disease, this is caused by deficiency of AVP secretion (central DI)
- Replacement is with desmopressin (DDAVP)
- Administered iv/im acutely, chronically as tablet or nasal spray

- Starting dose (oral tablet) 100-200 μg nocte, increasing as required up to 200 μg tid
  - 10 μg nocte usual starting dose if using nasal spray

- Monitor thirst, urine output, serum Na
- Allow one morning a week of delaying administration to allow breakthrough polyuria
- Tablets cause less hyponatraemia than nasal spray

Answers

- Amenorrhoea – commence oestogen/progestin
- Fatigue – unaddressed GH deficiency, hydrocortisone excess, inadequate thyroxine??
- Weight gain – is she taking too much hydrocortisone? Reduce dose. Effect of GH deficiency?
- Thirst/polyuria – optimise desmopressin dose regimen

Optimising pituitary replacement therapy (1)

- Discussion was had regarding best form of sex steroid replacement.
- Advised to avoid the oral contraceptive pill
- Transdermal E_2 - initially 50 μg, for first 3 months then 100 μg oestradiol patch weekly
- Mirena IUD as the progestin, replacing her previous copper IUD
- No withdrawal bleeds expected.

Optimising pituitary replacement therapy (2)

- Hydrocortisone dose was reduced
  - From 24 mg/day (10/10/4) to 16 mg (8/4/4)
- Thyroxine dose was adequate with free T4 in the middle of the normal range 15 pmol/L (ref range: 10-20)
  - 75 μg/day
- GH started at 0.3 mg/day sc injection
  - Self funded
- Desmopressin – regimen altered to 200 μg bd, then tid
  - Resulted in good control of the polyuria

Outcome 18 months post-op

- "I feel normal"
- Studying PhD in neuroscience
- Weight reduced by 4kg to 55.3 kg
- Medications doses remain stable
- No clinical features of glucocorticoid excess or deficiency

- Na 140 mmol/L
- T4 14 pmol/L (ref range 10-20) TSH <0.05
- IGF-1 26 nmol/L (ref range 17-42)
- E_2 concentration 210 pmol/L