Update On The Management Of Pituitary Disease

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Presentation Outline

• ACTH deficiency
  - Diagnosis
  - Management

• Genetic causes of pituitary adenomas
Anterior Pituitary Hormones

- Pituitary

Adenoma

- ACTH → Adrenal gland
- TSH → Thyroid
- LH → Ovaries
- FSH → Testes
- GH → Growth
- Prolactin → Breast milk

?
Hypothalamic-Pituitary-Adrenal Axis

- **Hypothalamus**
  - CRH
- **Pituitary**
  - ACTH
- **Adrenal**
  - Cortisol

- **Important role in day-to-day physiology**
  - Stimulates appetite
  - Fat, muscle and bone mass
  - Insulin sensitivity and secretion
  - Regulates blood pressure

- **Critical role during major illness/surgery**
  - Essential to maintain blood pressure
  - Lack of cortisol can be fatal

- Adrenal Cortisol

- Hypothalamus

- CRH

- Pituitary

- ACTH
Pituitary Adenomas And HPA Axis

- Pituitary adenomas can compress the remainder of the pituitary gland and cause hypopituitarism
- Some patients pituitary function improves after pituitary surgery
- Sometimes the normal pituitary gland is damaged during pituitary surgery
- It is imperative that pituitary function is assessed before and after pituitary surgery
Assessment Of HPA Axis

- Morning cortisol
- Short synacthen test
- Insulin tolerance test
- Metyrapone test
Morning Cortisol

- Cortisol > 450 nmol/L: Intact HPA axis
- Cortisol < 100 nmol/L: HPA deficiency

Debono M et al. J Clin Endocrinol Metab 1994
Short Synacthen Test

- Tests adrenal function
- Best test for primary adrenal insufficiency
- False negatives with acute hypopituitarism
- ? Lacks sensitivity to detect mild ACTH deficiency
- Large UK survey reported safely predicts risk of adrenal crisis in most patients*

* Agha A et al. J Clin Endocrinol Metab 2006
Insulin Tolerance Test

- Tests the integrity of the entire HPA axis
- Considered the gold standard
- Requires more resources than synacthen test
- Small risk of seizure or loss of consciousness (1 in 500)

↓ glucose

Hypothalamus

CRH

Pituitary

ACTH

Adrenal

Cortisol

* Agha A et al. J Clin Endocrinol Metab 2006
Metyrapone Test

- Tests the entire HPA axis
- Risk of adrenal crisis
- Assay not routinely available
Australasian Practice

• Questionnaire to 18 tertiary hospitals in Australia and New Zealand performing pituitary surgery. Definitive post-operative testing of HPA axis
  – Eight insulin tolerance test (44%)
  – Four 250 µg synacthen test (22%)
  – One 1 µg synacthen test (6%)
  – Two metyrapone test (11%)
  – Three early morning cortisol (17%)

Summary: Diagnosis Of ACTH Deficiency

- Pituitary adenomas can increase pressure in the pituitary fossa and cause ACTH deficiency.
- It is critical that patients be assessed for ACTH deficiency pre- and post-operatively.
- Opinions differ as to how best to do this, with wide variability in Australasian practice.
Presentation Outline

- ACTH deficiency
  - Diagnosis
  - Management
- Genetic causes of pituitary adenomas
Normal Cortisol Production

- Before 1990, it was thought that most humans made 30 mg hydrocortisone every day

![Graph showing cortisol production rate](image)

Esteban N et al, J Clin Endocrinol Metab, 1991
Choosing Glucocorticoid Doses

- Weight-based dosing*
- Serum cortisol 4 hours after morning hydrocortisone*
- Cortisol day curve
- Urinary free cortisol unhelpful
- Clinical judgement
- A biomarker of glucocorticoid activity is badly needed

* Mah PM et al. Clin Endocrinol, 2004
Glucocorticoid Dose And Mortality

Non-functioning adenoma
All cause mortality

Acromegaly
All cause and CV mortality

Zueger et al. JCEM 2012

Sherlock et al. JCEM 2009
Glucocorticoid Dose And Vascular Function

- 17 hypopituitary subjects were studied before and after a 7-day increase in hydrocortisone dose to 30 mg/day

Endothelial function

![Bar graph showing endothelial function before and after increased glucocorticoid dose.](Image)

* p = 0.04

Petersons C et al. J Clin Endocrinol Metab 2014
Glucocorticoid Dose Reduction

- 11 hypopituitary subjects studied before and after a 6 month reduction in hydrocortisone from >20 to 10-15 mg/day
- Reduction in total and central fat mass, cholesterol and triglycerides and improved quality of life

Danilowicz K et al, Pituitary, 2008
New Glucocorticoid Formulations

- **Plenadren**
  - Tablet with an immediate-release coating combined with an extended-release core
  - Once daily dosing
  - Approved for use in European Union

- **Chronocort**
  - Modified-release hydrocortisone
  - Twice daily dosing
  - Better replicates circadian cortisol production
Normal Cortisol Secretion

Debono M et al. J Clin Endocrinol Metab 1994
Plenadren Pharmacokinetics

Johannsson G et al, J Clin Endocrinol Metab, 2012
Clinical Effects Of Plenadren

• In a 12 week crossover study, Plenadren reduced weight, systolic and diastolic blood pressure and glycosylated haemoglobin compared to conventional hydrocortisone

Johannsson G et al, J Clin Endocrinol Metab, 2012
Summary: Glucocorticoid Replacement

- Mean daily cortisol production is about 10 mg/day
- Hydrocortisone doses above 25-30 mg/day are associated with increased mortality
- Reducing high glucocorticoid replacement doses improves surrogate markers of cardiovascular disease
- New glucocorticoid replacement regimens that better replicate normal cortisol physiology are being developed

I treat most patients with 15-20 mg/day in two or 3 divided doses
Presentation Outline

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• Genetic causes of pituitary adenomas
Familial Pituitary Tumour Syndromes

- Multiple endocrine neoplasia 1 syndrome
- Carney complex
- McCune Albright syndrome
- SDH-related pituitary tumours
- *Familial Isolated Pituitary Adenomas* (FIPA)
Familial Isolated Pituitary Adenomas (FIPA)

• First described in the late 1960’s
  - More than 200 families described
• Tumours isolated to the pituitary
  - PRL (41%), GH (30%), NFA (17%), Cushing’s (4%)
  - Different types amongst family members
• Cause of most cases with FIPA is unknown
• 20% of patients with FIPA have mutations in AIP gene
John Hunter and The Irish Giant

John Hunter

Charles Byrne
Gigantism

- Develop GH secreting tumour after epiphyseal plates are closed = acromegaly
  - Mean age diagnosis 40-45 years
- Develop GH secreting tumour before epiphyseal plates are closed = gigantism

If you develop a rare tumour at an atypical (young) age, this suggests there could be an underlying genetic predisposition
John Hunter (1728 – 1793)

• Born in Scotland, worked in London
• Superb anatomist
• Father of scientific surgical research
• Trained Edward Jenner in scientific research, inventor of small pox vaccine
• Expert in venereal disease, inoculated himself with gonorrhea and syphilis
• Collector of plant, animal and anatomy specimens, the Hunterian Museum is in the Royal College of Surgeons, London
Charles Byrne (1761 – 1783)

• Born in Littlebridge, Northern Ireland
• Height at death = 2.31 m (7 foot 7 inches)
• Made a fortune entertaining the public in London
• Died aged 22 from alcoholism and tuberculosis
• Planned for his death. He requested
  – Body sealed in lead coffin
  – Watched by friends day and night
  – Sunk deep in the sea

De Herder W. Pituitary 2012
Back To John Hunter

• Wanted Charles Byrne’s skeleton for his museum
• Employed a detective to keep watch on Byrne’s whereabouts and health
• Obtained Charles Byrne’s skeleton during the 75 mile voyage from London to the seaside town of Margate
• Rumoured he paid the undertaker 500 pounds to hand over the skeleton
Fast Forward To 1909

- Harvey Cushing opened the skull of John Byrne and noted that the pituitary fossa was enlarged.
- Concluded that Charles Byrne had gigantism secondary to a pituitary tumour.

Chahal H et al. NEJM 2011
Fast forward 2010

- 4 Northern Irish families identified with same *AIP* mutation (c.910C→T)
- Could they be related to the Irish Giant?

Chahal H et al. NEJM 2011
2010 Continued

- DNA extracted from two of Charles Byrnes teeth
- Found to also carry c.910C→T mutation

### Microsatellite analysis

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- Minimal common region: 2.68 Mb
- Rutgers map: 1.74 cM
- HapMap map: 1.15 cM

Chahal H et al. NEJM 2011
Further Projections

- Common ancestor ~57 generations ago
- Expected number of carriers in one generation ~68
- Numbers of mutation carriers in currently living family could be several hundred

Chahal H et al. NEJM 2011
What Is AIP?

- AIP = Aryl hydrocarbon receptor interacting protein
- Gene is on chromosome 11
- Encodes a 330 amino acid protein that suppresses tumour formation
- Mutation in AIP leads to loss of tumour suppressor function and increased tumour formation
- >60 mutations described to date
Clinical Features Of AIP Mutations

- 96 patients with AIP mutations
  - 75 GH-secreting tumour
  - 13 prolactinoma
  - 7 non-functioning adenoma
  - 1 TSH-secreting adenoma
- More aggressive, frequently invasive tumours
- Younger age of diagnosis
- Often resistant to medical therapy

Daly et al. JCEM, 2010
Genetics Of AIP Mutations

- Autosomal dominant inheritance
- Penetrance = 50%

Chahal H et al. NEJM 2011
Who To Screen For AIP Mutation

- Patients with familial isolated pituitary adenoma
- Patients with any pituitary adenoma arising before age 18 years
- Patients with pituitary macroadenoma arising before age 30 years

Family History Of AIP Mutation

- Algorithms still being optimized
- Consider genetic testing from age 4 years
- If AIP negative, no further testing
- If AIP positive
  - Height velocity yearly (children)
  - Pituitary function tests yearly until age 30 years and then less frequently
  - MRI 5 yearly until age 30 years and then less frequently

Summary: Genetics

• Understanding of the genetics underlying development of pituitary adenomas is rapidly progressing
• AIP mutations account for about 20% of familial isolated pituitary adenomas
• The history of gigantism has contributed to our understanding of pituitary tumour genetics and makes a pretty interesting story