

The 10th Clinicopathological Conference on Pituitary Disease

Royal College of Physicians, London, 6th March 2008

Programme

9:25 Welcome and Introduction Mr Michael Powell (London)

9:30 Keynote Lecture

Hypopituitarism following brain injury – Are we failing our patients?
Dr Stephanie Baldeweg (London)

10:20 Forum 1 - Cases – Pituitary disease and Pregnancy

Chair: Dr Mark Vanderpump (London) and Mr Michael Powell (London)

(Cases will be presented at approximately ten to fifteen-minute intervals)

Panel:	Professor John Monson	Endocrinology, London
	Dr Paul Carroll	Endocrinology, London
	Professor Karim Meeran	Endocrinology, London
	Dr Andrew Toogood	Endocrinology, Birmingham
	Dr William Drake	Endocrinology, London
	Dr James Ahlquist	Endocrinology, Southend
	Dr Nick Plowman	Radiotherapy, London
	Dr Andy Platts	Neuroradiology, London
	Professor William Couldwell	Neurosurgery, Utah, USA
	Professor Nicolas de Tribolet	Neurosurgery, Geneva, Switzerland
	Mr Kanna Gnanalingham	Neurosurgery, Manchester
	Mr Simon Cudlip	Neurosurgery, Oxford

1. Enlargement of prolactinoma in pregnancy

Fadl A, Thebo Z, Chakovarati S, Pollock J, Khatami S, Chawda S & Stojanovic N (Romford)

2. A rare case of hypoprolactinaemia in pregnancy

Martin A & Russell-Jones D (Guildford)

3. Pituitary apoplexy, prolactinoma and pregnancy

Moyes VJ, Alusi G, Sabin HI, Sanghi A & Akker SA (London)

4. Recurrent lymphocytic hypophysitis in pregnancy

Suresh D & Baldeweg SE (London)

5. Monitoring for Nelson' syndrome in pregnancy

Ghaffer A, Martin NM, Hatfield EC, Mehta A, Mendoza N, Roncaroli F & Meeran K (London)

11:20 Coffee and Posters

11.50 Keynote Lecture

Chemotherapy for aggressive pituitary tumours

Dr Nick Plowman (London)

12.10 Forum 2 – Cases - Acromegaly

Chair: Dr Stephanie Baldeweg (London) and Miss Joan Grieve (London)

6. A case of acromegaly and Chiari malformation – treatment dilemmas
Gnanalingham K, Kearney T & Davis J(Manchester)

7. An interesting case of acromegaly
Waterhouse M, Sabin I, Plowman N, Akker S & Chowdhury T (London)

8. Is hyperprolactinaemia with acromegaly due to dual secretion or stalk compression:
Cabergoline or surgery as first-line treatment?
Saha S, Lecamwasam VL, Bassett JHD & Todd J (London)

9. DIY treatment of acromegaly
Morganstein DL, Hatfield EC, Martin NM, Mehta A, Mendoza N & Meeran K (London)

13.00 Lunch and Posters

13.45 Forum 3 – Miscellaneous Pituitary Cases

Chair: Dr James Ahlquist (Southend) and Dr Gerard Conway (London)

10. Pituitary apoplexy – When is surgery indicated?
Nelson RJ, Park N & Hardie R (Bristol)

11. Spontaneous resolution of a recurrent pituitary adenoma and its associated endocrine and neuro-ophthalmic abnormalities in previously treated Cushing's disease
Gholap N & Page SR (Nottingham)

12. Two contrasting TSHomas and a managerial challenge
Vithian K, Powell M & Ahlquist J (Southend and London)

13. Pitfalls in the diagnosis of a thyrotrophinoma
Joharatnam J, Martin NM, Hatfield EC, Roncaroli F, Mehta A, Mendoza N & Meeran K (London)

14. Challenges in the management of an unusual pituitary tumour
Raja Ali RA, O'Sullivan F, Murray M, Sabin I, Drake WM, Al-Saraj S & Bell SM (Galway and London)

15. Malignant prolactinoma
Leelarathna L, Powell M, Carroll P & Thomas S (London)

16. Pituitary Cushing's or ectopic ACTH secreting tumour?
Nethaji C, Powell M., Baldeweg SE (London)

17. Aggressive Cushing's disease with cavernous sinus involvement – what to do next?
Graggeber J, Burnett NG, Pickard JD, Simpson H, Morris DG & Gurnell M (Ipswich/Cambridge)

15.30 Afternoon Tea and Posters

16.00 Keynote Lecture

Surgery in the cavernous sinus for functioning pituitary tumours
Professor William Couldwell (Utah, USA)

16.30 Close

Posters

Panhypopituitarism resulting from a neuroendocrine tumour
Duggal T (East Surrey)

A challenging case of macroprolactinoma in adolescence
Myint KS, Williams R, Acerini C, Pickard JD, Chatterjee VKK, Wood DF, Gurnell M & Simpson HL
(Cambridge)

A hole in one
McGowan B, Caputo C, Hatfield EC, Martin NM, Mehta A and Meeran K (London)

Cabergoline treatment of a macroprolactinoma in pregnancy does not preclude breast feeding.
Chaudhri OB, Martin NM, Hatfield EC, Mehta A & Meeran K (London)

Recurrence of Cushing's disease?
Ghaffar A, Martin NM, Hatfield EC, Mehta A, Mendoza N, Roncaroli F & Meeran K (London)

Bitemporal hemianopia: not always the case with macroadenomas
Cegla J, Martin NM, Mehta A, Mendoza N, Hatfield EC & Meeran K (London)

A case of recurrent ependymoma
HS Chahal, R Belcher and AB Grossman (London)

The man with two concurrent pituitary tumours
Sharma S, Artham S, Gorick S, Powell M, Dhatariya K (Norwich and London)

Case of secondary hypogonadism secondary to multi focal astrocytoma involving hypothalamus
Ulahannan T & Thiel A (Gloucester)

Acute pituitary failure due to a non-functioning pituitary tumour presenting with intractable post-operative vomiting
Ali Abbara , Dr Abdul F A Lakhdar (Whipps Cross University Hospital, London)

A large TSH and Growth Hormone secreting pituitary tumour in a young man , - challenges for endocrinologists and surgeons.
Nick Phillips, (Leeds)

Pituitary abscess
Charles Taylor, (Kings College Hospital, London)

The man with two concurrent pituitary tumours:
Sharma, Satish Artham¹, Sondra Gorick¹, Michael Powell², Ketan Dhatariya¹ (Norwich & London)

An unusual presentation of a prolactinoma
GDS Anandappa, (Luton)

Programme Organising Committee March 2008

Dr James Ahlquist Dr Stephanie Baldeweg
Dr Gerard Conway Ms Joan Grieve
Mr Michael Powell Dr Mark Vanderpump

Forum 1- Pituitary disease and Pregnancy

Chair: Dr Mark Vanderpump (London) and Mr Michael Powell (London)

1. Enlargement of prolactinoma in pregnancy

Fadi A, Thebo Z, Chakovarati S, Pollock J, Khatami S, Chawda S & Stojanovic N (Romford)

The management of macroprolactinomas in pregnancy can be difficult. A 29 year old lady with a previously diagnosed macroprolactinoma transferred her care to our unit in 20th week of pregnancy. She was on Cabergoline 1mg twice weekly at that time. Pituitary MRI around 20th week of pregnancy showed a tumor displacing but not compressing the optic chiasm. Her visual fields were initially normal, but deteriorated after the 34th week of pregnancy. Pituitary MRI repeated at that time showed a significant tumor enlargement. A healthy baby girl was delivered by ventouse in 35th week of pregnancy. Patient's visual fields improved dramatically after the delivery, and her dynamic pituitary tests were normal. She has now contemplating pituitary surgery. Data about the use of Cabergoline throughout pregnancy are relatively sparse. We would value panel's opinion on management of the patient's eventual further pregnancies and the optimal mode of delivery in patients whose vision is compromised by pituitary macroadenomas.

2. A rare case of hypoprolactinaemia in pregnancy

Martin A & Russell-Jones D (Guildford)

A previously fit 31 year old woman (Para 0 +1) presented in the ANC at 35 weeks gestation with a 3-week history of rapidly progressive patchy bitemporal hemianopia. A MRI of the pituitary with gadolinium showed a diffusely enhancing homogenous mass (16mm) in the adenohypophysis with suprasellar extension distorting the optic chiasm. The sellar floor was deep but not eroded. No macroscopic cavernous sinus involvement, hydrocephalus or cerebral oedema noted. Blood results confirmed she had anterior pituitary hormone dysfunction including prolactin deficiency which is rare (IGF 1 9.3, prolactin 86, TSH < 0.03, T3 5.6, cortisol 114, LH 3, Na 142, K 4.9, urea 5.5, creat 87). A presumptive diagnosis of lymphocytic hypophysitis with panhypopituitarism was made. Hydrocortisone and thyroxine replacement therapy were initiated immediately and she was delivered within 24 hours by LSCS in anticipation to pituitary surgery. Two weeks post partum she had complete resolution of symptoms and MRI proven shrinkage of the tumour with no chiasmal compression (13mm). Pituitary surgery was postponed. Her menstrual cycles resumed at 9 weeks postpartum and she was successfully weaned of thyroxine and steroids. At 6 months she had normal formal visual fields and a MRI pituitary showed minimal pituitary enlargement. Anterior pituitary function tests including synacthen and TRH tests were normal. She has had regular follow up in the endocrine clinic and is now 20 weeks pregnant. Interestingly despite being pregnant, her prolactin level is sub-physiological. She is awaiting a MRI of the pituitary and it would be interesting to see if her pituitary disease has recurred. The therapeutic approach to these patients is widely varied and controversial. Some argue that the disease is often self-limiting and a conservative approach is justified in most cases. Transsphenoidal surgery is sometimes applied as first line treatment particularly in those who present with rapid visual loss but this invasive approach carries obvious risks to the patient and fetus. Little is known about the natural history of the disease and there are no set diagnostic criteria in place for patients with suspected new or recurrent lymphocytic hypophysitis. What are the predictors of disease severity? The therapeutic approaches vary widely and are often controversial. There are a few reported cases of recurrent lymphocytic hypophysitis in subsequent pregnancies. What should we be advising these patients about the risk of recurrence in future pregnancies?

3. Pituitary apoplexy, prolactinoma and pregnancy

Moyes VJ, Alusi G, Sabin HI, Sanghi A & Akker SA (London)

A 35-year-old female Ghanaian barrister presented with headaches, blurred vision and secondary amenorrhoea. Prolactin was 4400miu/l with no significant macroprolactin and a right temporal visual field defect was detected. Anterior pituitary function was normal. MRI revealed a 2x2cm pituitary macroadenoma with bowing of the chiasm and ring enhancement suggestive of a cystic component.

Cabergoline was commenced with improvement in visual fields and prolactin fell to 1052miu/l with significant shrinkage of the prolactinoma on repeat MRI. After nine months of treatment, the patient unexpectedly became pregnant in Ghana and she discontinued the Cabergoline. At 20/40 she developed recurrent headaches and vomiting; visual fields and acuity were normal. Two doses of Bromocriptine were taken but discontinued due to nausea. At 27/40 she returned to UK and developed severe headaches and a mild concentric field defect. MRI showed a large pituitary mass with bowing of the chiasm and a fluid level, possibly haemorrhagic or cystic change. Prolactin was 9117miu/l and ACTH and TSH deficiency were noted and replacement commenced with resolution of her symptoms. The relative risk to the mother's vision versus the risk of early intervention to the fetus, were discussed between endocrinologists, pituitary surgeon, ophthalmologist, anaesthetist, paediatrician, obstetrician and patient. Bromocriptine was commenced in the hope of shrinking the cellular component and removing chiasmal compression. Prolactin fell to 2927miu/l and visual perimetry improved. At 30/40 she developed sudden onset right sided headache and bitemporal hemianopia. Visual acuity was unchanged. Dexamethasone was commenced and Bromocriptine replaced with Cabergoline. Symptoms improved but without a detectable improvement in visual perimetry. At 34/40 a reduction in visual acuity was detected and TSS was performed; a large volume of blood with no identifiable pituitary tissue was removed. Visual fields and acuity fully recovered post-operatively. Emergency LSCS was performed at 36/40 for anhydramnios and a healthy baby boy was delivered. This case of pituitary apoplexy in a pregnant woman with a background of macroprolactinoma raises several questions regarding antenatal management. Should Bromocriptine be continued where suprasellar adenomas have become intrasellar at conception? Would Bromocriptine have reduced the risk of haemorrhage? When is the optimal time for intervention in view of the risk of preterm labour and viability of the fetus? How long can the chiasm be compressed before permanent visual dysfunction develops?

4. Recurrent lymphocytic hypophysitis in pregnancy Suresh D & Baldeweg SE (London)

Lymphocytic hypophysitis is a rare inflammatory disease of the pituitary gland. The aetiology is unknown though probably of autoimmune origin. This condition usually occurs in women during pregnancy or in the post-partum period. Recurrent disease in pregnancy is rare. We present a 35 year old patient of African origin who initially presented in 2004 at 12 weeks gestation with headaches, a third nerve palsy but no visual field defects. She responded to high dose steroids. A healthy baby was delivered. Post partum she developed galactorrhoea responsive to Cabergoline 500 micrograms twice a week. She also developed secondary hypothyroidism treated with thyroxine 50 micrograms daily. Treatment with low dose steroids (Prednisolone 5 mg) was continued. Steroid withdrawal was hampered by severe headaches. Before receiving family planning advice she had an unplanned conception in 2006 with a spontaneous abortion. Repeat pituitary MRI showed resolving Hypophysitis. She discontinued all medication and again become pregnant in 2007. Visual fields and cranial nerves were normal at 16 weeks gestation. She was again commenced on Prednisolone 5mg and Thyroxine 50 micrograms daily. At 24 weeks gestation MRI showed a dramatic increase in pituitary size with supra sellar extension. Visual field plotting showed right homonymous hemianopia. Prednisolone dose was increased to 40 mg once daily. At 33 weeks her symptoms improved with complete normalization of her visual fields. Recurrent lymphocytic hypophysitis in pregnancy is rare. The clinical course may be complicated, emphasizing the need for rigorous long-term observation in the preconception stage and during pregnancy. Corticosteroids are the therapy of choice in the inflammatory stage and should be undertaken as soon as the diagnosis has been established. Regular multi-disciplinary surveillance is required.

5. Monitoring for Nelson' syndrome in pregnancy Ghafter A, Martin NM, Hatfield EC, Mehta A, Mendoza N, Roncaroli F & Meeran K (London)

A 21-year-old woman was referred to our unit in 2003 for investigation of possible Cushing's syndrome. She had bruising, abdominal striae and had gained weight over a 5-year period. ACTH-dependent Cushing's syndrome was confirmed on low-dose dexamethasone suppression testing (LDDST): ACTH

37.9 ng/L, T = 48 cortisol 79 nmol/L. A central source of ACTH was confirmed by bilateral inferior petrosal sinus sampling (stimulated central to peripheral ACTH ratio was >3, inter-sinus gradient L:R >2 supporting a left sided pituitary source). Her pituitary MRI was normal. The patient underwent transsphenoidal surgery in Feb 2005. Histology confirmed a corticotroph adenoma. Post-operative cortisol on day 5 was 456 nmol/L. but there was some ambiguity about whether hydrocortisone had been taken before this measurement. Therefore, a LDDST was performed one month post-operatively which demonstrated cortisol suppression to 35 nmol/L, suggesting remission. An ITT performed six weeks post-operatively demonstrated a peak cortisol of 570 nmol/L. Approximately eighteen months later, she complained of increased hirsutism, low mood and bruising. She underwent two LDDSTs, a month apart, which showed 48 hr cortisols of 95 and 98 nmol/l respectively consistent with relapse. A pituitary MRI demonstrated a small 4mm cystic midline lesion in the pituitary. She elected to undergo a bilateral adrenalectomy to preserve fertility and this was performed laparoscopically in November 2006. Plasma ACTH just prior to her adrenalectomy was 85.7 ng/L. She commenced Hydrocortisone and Fludrocortisone replacement post-operatively. A repeat pituitary MRI in August 2007, showed an increase in the cystic area to 6mm. In view of this finding we planned to measure a plasma ACTH 2 hours after her morning hydrocortisone. However, on contacting her, she informed us that she was pregnant, making ACTH difficult to interpret. An MRI Jan 2008 scan performed in the second trimester of pregnancy did not show any further increase in size of the pituitary lesion, and visual fields have remained normal.

Our questions to the expert panel are:

- 1) In view of the doubling of the volume of her pituitary adenoma over a one year period and the difficulty interpreting her ACTH in pregnancy, should we aim to repeat her pituitary MRI in the third trimester?
- 2) In view of increasing placental CRF as pregnancy progresses, is there an increased risk of her developing Nelson's syndrome during her pregnancy?

Forum 2 - Acromegaly

Chair: Dr Stephanie Baldeweg (London) and Miss Joan Grieve (London)

6. A case of acromegaly and Chiari malformation – treatment dilemmas Gnanalingham K, Kearney T & Davis J(Manchester)

We describe a 27-year-old woman, with chronic headaches, and a 6 month history of peripheral visual loss and diplopia. She was also known to have right sided carpal tunnel syndrome, Raynaud's phenomenon, hypertension and congenital feet clubbing. She was very tall, with facial features of acromegaly and had bitemporal visual field deficits. Acromegaly was confirmed biochemically (raised IgF-1 536nn/ml and GH nadir on OGTT of 4.7 mU/L). MR scans of brain and cervico-thoracic spine revealed multiple abnormalities including atypical pituitary fossa appearances, a 2x1 cm suprasellar lesion causing chiasmal compression, Chiari type I malformation and a small syrinx in the cervico-thoracic cord. Clinically, the suprasellar lesion appeared to be more symptomatic. She underwent an extended endoscopic transsphenoidal resection of the suprasellar lesion, in conjunction with a temporary lumbar drain for post-op CSF diversion. A sparsely granulated GH cell adenoma was confirmed histologically. Post-operatively, her bitemporal visual field loss was worse and she also developed a low grade meningitis that responded to antibiotic treatment. Post-op GH nadir on OGTT was less than 0.1 mU/L confirming disease remission. At 2-3 weeks after surgery, the patient suffered 2 episodes of sudden loss of consciousness, requiring intubation and ventilation. Initially an external ventricular drain was placed and later a foramen magnum decompression was carried out. She made slow neurological recovery and is independent at 6 months follow-up. There are several discussion/learning points in this case, regarding the choice and type of intervention undertaken. Surgery for pituitary adenomas in patients with posterior fossa pathology should be undertaken with caution. Even if the Chiari malformation is asymptomatic at presentation, after transsphenoidal surgery it may not be so.

7. An interesting case of acromegaly

Waterhouse M, Sabin I, Plowman N, Akker S & Chowdhury T (London)

In November 2005, a 31 year old, white caucasian woman presented to the emergency department with abdominal pain and nausea. She described significant weight loss and osmotic symptoms over the preceding 2 months. She had no significant past nor family history of disease. A diagnosis of type 1 diabetes mellitus complicated by diabetic ketoacidosis was made. This was based on heavy ketonuria, an arterial ph 7.2 kPa and venous glucose 24.8mmol/l. The HbA1c was 12.7% and her GAD autoantibodies were negative. She weighed 85kg at presentation. She was treated conventionally and then converted to a basal bolus insulin regime requiring 200 units of insulin/ day. On review by the endocrine team, she was noted to have features characteristic of acromegaly with a bitemporal hemianopia. This was confirmed with a spot growth hormone (GH) level 197miu/l, IGF-I 1001ng/ml (age related normal range 56 – 280 ng/ml, median 176ng/ml) and a mean GH burden of 250miu/l on 5 point testing ACTH and gonadotrophin deficiency were diagnosed and she was commenced on replacement. Imaging revealed a pituitary macroadenoma extending to the optic chiasm and laterally into the sphenoid sinus. She went on to have transsphenoidal hypophysectomy followed by external beam radiotherapy and medical therapy with Cabergoline. There was only a modest reduction in the GH burden; IGF1 897ng/ml. She was intolerant of somatostatin analogues and was commenced on Pegvisomant with dose titration up to maximum dose. The IGF-I fell to 450ng/ml in response. She developed hypoglycaemia and insulin therapy was discontinued in May 2007. An oral glucose tolerance test confirmed that she no longer had diabetes mellitus (OGTT: Time 0 glucose 4.4mmol, 120 min glucose 3.0mmol/l). In October 2007, she underwent gamma knife radiosurgery targeted to the remaining pituitary disease. Her most recent IGF1 is 253ng/ml (median 176 ng/ml). We think that this case illustrates the challenges involved in managing aggressive acromegaly, taking 2 years to lower the IGF-1 into the normal range. In addition, it raises questions regarding the pathogenesis of the ketosis-prone diabetes and the role of the very high levels of GH and IGF-1.

8. Is hyperprolactinaemia with acromegaly due to dual secretion or stalk compression: Cabergoline or surgery as first-line treatment?

Saha S, Lecamwasam VL, Bassett JHD & Todd J (London)

A 56-year-old gentleman was referred with a 3 year history of increasing fatigue and lethargy. He had noticed that his feet had become swollen and that his ring size had increased so that he could no longer wear his wedding ring. He had noticed some increased sweating over the last 1-2 years and he had gained about 3 stone in weight over this time. He denied any change in his sexual function, headaches or visual changes. He had a past history of hypertension and peptic ulcer disease. There was no relevant family history. Drug history included Thyroxine 100ug (started by his GP 2 months earlier), Amlodipine 10mg and Simvastatin 40mg. On examination, his BP was 142/76 lying and standing, there were no specific features of acromegaly and his secondary sexual characteristics was normal. His visual fields were full to confrontation. Random bloods showed an elevated prolactin at 4667 uM/L (NR 0-325), growth hormone (GH) at 15.5 mU/L and IGF-1 110 nmol/L (NR 13-64) with secondary hypogonadism (LH 5.4 IU/L, FSH 6.6 IU/L, testosterone 4.9 nmol/L (NR 10-26)). He also had a low 9 a.m. cortisol at 198 nmol/L with an ACTH 17.5 ng/L. His TFT's showed a FT4 11.8 pmol/L, FT3 5.5 pmol/L and TSH <0.05 mU/L (on Thyroxine). The GH failed to suppress on OGTT (mean GH 13.8 mU/L) and there was an inadequate cortisol response on glucagon stress test (peak cortisol 158 nmol/L) confirming secondary hypoadrenalism. The pituitary MRI showed a large microadenoma (8.9mm) invading the left cavernous sinus. These findings are in keeping microadenoma that is secreting both GH and prolactin or a GH secreting microadenoma with pituitary stalk compression leading to hyperprolactinaemia. He was commenced on Hydrocortisone replacement. The patient was not keen to have surgery and, after discussion in our pituitary MDT, he was commenced on Cabergoline, at an initial dose of 0.25mg weekly, which will be increased according to his response, and with a view to reassess his GH and prolactin responses after 8 weeks on treatment. If the GH response is inadequate he will be referred for surgery at that time. We would be interested in the panel's views as to whether Carbergoline or surgery should be the first line treatment in this case?

9. DIY treatment of acromegaly

Morganstein DL, Hatfield EC, Martin NM, Mehta A, Mendoza N & Meeran K (London)

A 23-year-old woman who is a student presented to A&E with a three day history of worsening headache and vomiting. She was photophobic but afebrile and had no neck stiffness. The initial differential diagnosis included sub-arachnoid haemorrhage so a CT head was arranged which showed a large mass in the region of the pituitary fossa, without any evidence of blood. On further questioning she had a 6 month history of swelling of the hands and feet, which had been thought to represent an arthritic process. However there had been no increase in shoe size, previous headaches or sweating. She had been on the contraceptive pill but had stopped it six weeks previously and had one menstrual period since then. Initial investigations showed a random cortisol of 62 nmol/l and GH of 25.2 IU/ml, with an elevated IGF-1 of 167 IU/ml (13-64). Prolactin was 217, thyroid function was normal and oestradiol was 149nmol/l with normal gonadotrophins. MRI confirmed a large pituitary mass with no evidence of haemorrhage. Visual fields were normal. She was commenced on glucocorticoid replacement and her headache and vomiting settled over the next 4 days. Two weeks later a random GH was 5.8 IU/ml with an IGF-1 of 116 IU/ml. fT4 and fT3 were now low with a TSH of 0.51 and her estradiol had become undetectable. After a further two weeks an OGTT was performed which showed a mean GH of 4.12 (nadir 1.4). Her IGF-1 had fallen further to 55 IU/ml. She had developed polyuria with plasma and urine osmolalities consistent with diabetes insipidus. In conclusion we describe a case where the first presentation of acromegaly was with a pituitary apoplexy, followed by the rapid development of pan-hypopituitarism. The initially elevated GH levels have fallen such that the IGF-1 has now normalised.

Our questions for the expert panel are:

- 1) What should be the next step in her management?
- 2) Should she now have surgery in an attempt to remove any remaining surgery, should we initiate medical management to further lower her GH or adopt a wait and see approach?
- 3) Is there a risk of future recurrence?

Forum 3 - Miscellaneous Pituitary Cases

Chair: Dr James Ahlquist (Southend) and Dr Gerard Conway (London)

10. Pituitary apoplexy – When is surgery indicated?

Nelson RJ, Park N & Hardie R (Bristol)

The indications for surgery; the optimal timing of surgery and the impact of surgical decompression on neurological recovery in patients presenting with pituitary apoplexy remain controversial. A 73-year-old man with a past history of a silent myocardial infarct and Type II diabetes, presented with a two week history of left shoulder pain and sudden onset of a left III n palsy. CT angiography and MRI scanning (under sedation) demonstrated a pituitary macroadenoma with cavernous sinus invasion and a 5 mm suprasellar 'nodule' abutting the chiasm. Occipital intraventricular blood without hydrocephalus was noted. Aspirin and clopidogrel were stopped. A random cortisol was 271 and prolactin 750. Corticosteroid therapy was commenced. Within 24hrs the patient had developed a right VI nerve palsy and within 48 hrs bilateral ophthalmoplegia, subtle upper quadrantic field loss and confusion. ECGs and troponin levels showed no evidence of acute cardiac ischaemia. A standard transnasal, transsphenoidal approach was undertaken encountering typical infarcted pituitary tissue invading the sphenoid mucosa and bone. The pituitary fossa was fully decompressed. The patient's post-operative recovery was uneventful. Histology confirmed acute infarction in a sparsely granulated prolactin-staining adenoma. The following day the right ptosis had improved. On the second post-operative morning the patient suffered an unheralded cardiac arrest. Resuscitation was not successful. A post mortem showed no acute cardio-respiratory pathology. There was evidence of a little fresh haemorrhage around the pituitary stalk and III ventricle.

Discussion

- Should surgical decompression be undertaken in pituitary-apoplexy patients with ophthalmoplegia but no major visual loss?

- Is sudden death a feature of pituitary apoplexy in the absence of acute hydrocephalus or endocrine disturbance?
- Is the hypothalamic-sympathetic axis implicated?

11. Spontaneous resolution of a recurrent pituitary adenoma and its associated endocrine and neuro-ophthalmic abnormalities in previously treated Cushing's disease **Gholap N & Page SR (Nottingham)**

Spontaneous resolution of a pituitary adenoma is uncommon and seen mainly in non-functioning adenomas following pituitary apoplexy. We report a similar phenomenon in a patient with a recurrent ACTH-secreting adenoma, which was associated with a spontaneously resolving cavernous sinus syndrome. Pituitary-dependent Cushing's disease was confirmed in a 40-year-old lady in June 1999 following an initial presentation with poorly controlled type 2 diabetes and resistant hypertension. Pituitary MRI scanning revealed a left sided pituitary microadenoma which was treated by transsphenoidal surgery in February 2000. Serial postoperative MRI scans in 2001 and 2003 did not show residual tumour and her clinical and biochemical parameters were consistent with disease remission. Interestingly she still needed six different antihypertensive medications to achieve optimal blood pressure control. In July 2005 she presented with acute onset headache, vomiting, diplopia and complete ptosis and ophthalmoplegia in her left eye but with only minimally reduced visual acuity. An MRI scan revealed a recurrent pituitary tumour extending into the left cavernous sinus with features of haemorrhage into the tumour. Further pituitary surgery was not possible and she was referred for gamma knife radiotherapy at the regional centre. Over the subsequent 4 months her ptosis and ophthalmoplegia resolved completely, without radiotherapy. Repeat MR scanning on two occasions has confirmed complete regression of the recurrent tumour. Urinary free cortisol levels have remained within normal limits and her other pituitary function tests confirmed preserved endocrine function. Following the presumed pituitary apoplexy insulin therapy has been withdrawn and her diabetes remains well controlled on Glimepiride.

12. Two contrasting TSHomas and a managerial challenge **Vithian K, Powell M & Ahlquist J (Southend and London)**

TSHoma is a rare pituitary tumour which can present a significant management challenge. We report two contrasting cases, and would welcome discussion about further management of the second case.

Case 1: A 64 year old lady had tachycardia detected on a health check at her supermarket. She had palpitations, loose stools and weight loss. TFT showed TSH 6.36 mU/l, fT4 32.6 pmol/l (confirmed by re-assay using different methods), SHBG > 200 nmol/l, TPO negative. Pituitary function was otherwise normal. Pituitary MRI showed a 6-8 mm hypo-intense lesion in the left lobe. She was treated with thionamides with no significant benefit, and underwent transsphenoidal surgery; histology showed a pituitary adenoma with expression of both TSH and GH. Following surgery her thyroid function was normal, TSH 2 mU/l, fT4 13.9 pmol/l, fT3 2.9 pmol/l.

Case 2: A 38 year old man had tachycardia detected at a gym. TFT showed TSH 9.9 U/l, fT4 46 pmol/l, fT3 18.9 pmol/l, a subunit raised at 2.05 mU/l. Pituitary function was otherwise normal. Pituitary MRI showed a large tumour extending to the hypothalamus and brainstem behind a pre-fixed chiasm, giving a left homonymous hemianopia. He was treated with carbimazole 40 mg with modest benefit only. Two transsphenoidal operations have led to slight reduction in fT4 to 34.3 pmol/l, and complete loss of anterior pituitary function. He has had pituitary radiotherapy; an octreotide scan confirmed the presence of somatostatin receptors, and he has been treated with Sandostatin LAR to little effect, with fT4 still around 30 pmol/l. What further treatment would the panel recommend?

13. Pitfalls in the diagnosis of a thyrotrophinoma **Joharatnam J, Martin NM, Hatfield EC, Roncaroli F, Mehta A, Mendoza N & Meeran K (London)**

In January 2007, a 54 year-old woman was noted to have a bi-temporal superior quadrantanopia whilst undergoing a routine eye examination at her local hospital. Pituitary MRI revealed a large uniformly

enhancing sellar mass with extension both inferiorly into the sphenoid sinus and into the suprasellar cistern with chiasmatal compression. She was referred to our neurosurgical department and subsequently admitted for an elective transsphenoidal hypophysectomy. Our endocrine input was requested on the day prior to surgery. During our assessment, further questioning revealed a previous diagnosis of thyrotoxicosis 25 years ago. She was initially treated with anti-thyroid medication but went on to have a subtotal thyroidectomy. Post-operatively, she was prescribed Thyroxine, which was titrated gradually up to 300mcg per day. Subsequently she was lost to follow up. Twelve years later, she presented to her local hospital with a neck swelling and abnormal thyroid function tests (fT4 37.1 NR: 10-26 pmol/L, TSH 9.79 NR: 0.3-3.8mU/L). These results were attributed to poor compliance, although she denied this. A TRH test was performed and although this showed a blunted rise in TSH (baseline: 9.79, 60 mins 11.92), diagnosis of a thyrotrophinoma was considered too rare. In an attempt to improve her thyroid function test results, a combination of Thyroxine 300mcg and Liothyronine 20mcg was then prescribed. She was again lost to formal follow up until her presentation in 2007. Pre-operatively her TSH was 6.99, T4 32, LH 20, FSH 44, PRL 305. The patient was adamant that ever since her thyroidectomy, she had been fully compliant with her thyroid hormone replacement. Therefore we advised a graded T3 suppression test as well as a TRH test, to distinguish between a thyrotrophinoma and thyroid hormone resistance. The patient was unwilling to delay surgery in view of her visual field defect. As a result only a TRH test was performed. This confirmed a blunted TSH response (baseline: 6.30, 60 mins 8.37). SHBG was elevated at 138 (NR 30-100nmol/L). Both these results were consistent with a thyrotrophinoma, which was confirmed on post-operative histology. Post operatively a repeat MRI showed substantial reduction in tumour size. Serum TSH on day 4 was detectable at 0.28, fT4 13.1. Six weeks post-operatively a TRH test showed an inappropriately elevated baseline TSH with a blunted response (baseline: 6.07, 60 mins 9.10), consistent with remnant tumour. Therefore she commenced octreotide. Her TSH levels have been variable on octreotide, from 2.12-5.11 mU/L. We are currently discussing the option of radiotherapy treatment with her. When should we consider radiotherapy?

14. Challenges in the management of an unusual pituitary tumour

Raja Ali RA, O'Sullivan F, Murray M, Sabin I, Drake WM, Al-Saraj S & Bell SM (Galway and London)

A 62-year-old lady with seven year history of low grade multiple myeloma not requiring active treatment, presented in July 2007 with gradual onset of diplopia and partial left third nerve palsy. MRI brain showed a 3x2.9x2.3cm pituitary mass lesion. Baseline pituitary function tests were normal. Transsphenoidal surgery (TSS) was carried out in August 2007 and histology was reported as showing a benign pituitary adenoma. Postoperatively the patient reported improvement in symptoms but objectively had little resolution of the partial third nerve palsy. External-beam radiotherapy was planned. Two months later the patient re-presented with ocular pain and complete left third nerve palsy. MRI pituitary showed progression of the pituitary mass with involvement of the clivus and cavernous sinus. Further TSS was performed in the UK and histology confirmed the pituitary mass to be a myelomatous deposit. Re-review of the original histology also confirmed a myelomatous deposit. Haematological assessment of the patient did not reveal further evidence of disease progression. The patient is currently completing external-beam radiotherapy and is due to commence adjuvant systemic chemotherapy post-radiotherapy. This case illustrates the importance of a multi-disciplinary approach in an experienced pituitary unit when managing aggressive pituitary tumours. The opinion of the panel on further management of this unusual pituitary tumour in the event of future recurrence would be welcomed.

15. Malignant prolactinoma

Leelarathna L, Powell M, Carroll P & Thomas S (London)

28-year-old man presented in 1996 with a visual field abnormality and elevated prolactin (146000 mU/L). MRI demonstrated a pituitary macroadenoma compressing the optic chiasm & transsphenoidal surgery was performed on 17.02.1996 without a formal trial of dopamine agonist treatment. His post-operative prolactin was 32000 mU/L. Histology showed closely packed cells with hyperchromatic nuclei.

Immunocytochemistry revealed prolactin expression confirming a prolactinoma. Mitoses were seen within the tumour, often close together and histopathologist concluded that this tumour may recur. Dopamine agonist therapy was initiated with gradually increasing doses due to rising prolactin levels. In 2001 he underwent stereotactic radio surgery using the Leksell Gamma Knife for recurrent tumour growth. In November 2003 he was referred to our unit and by 2005, the prolactin rose despite high dose cabergoline therapy to peak of 42000 mU/L and he developed a right VI nerve palsy. MRI pituitary confirmed recurrent tumour centred in the right cavernous sinus and he underwent further transsphenoidal hypophysectomy. Histology showed a nested tumour composed of moderately pleomorphic cells. There was brisk mitotic activity. Tumour cells showed diffuse strong labelling with cytokeratin and prolactin. There was focal elevation of Ki67 labelling index - predictive of aggressive biological behaviour. After careful discussion with clinical oncologist, patient had a second gamma knife procedure in Oct 2005. The optic chiasm was kept to no more than 6 Gy as previous gamma knife delivered 8 Gy to the optic chiasm. His prolactin fell over the next 10 months from 45000 mU/L to 7000 mU/L. However 18 months after his second gamma knife, the prolactin rose again to 12000 mU/L despite continued high dose Cabergoline (2mg daily). MRI showed further recurrent tumour arising from the right parasellar region extending into the suprasellar region. A third transsphenoidal hypophysectomy was performed in August 2007, complicated by a significant CSF leak. Postoperatively he is being considered for Tamazolamide treatment. The prolactinoma has repeatedly grown despite high dose Cabergoline therapy and this tumour is probably no longer responsive to such therapy. He has had gamma knife twice and three transsphenoidal operations, last of which was complicated by significant CSF leak. Neither the patient nor the neurosurgeon is keen for any more surgery. What is the prognosis and best course of action for this young man?

**16. Pituitary Cushing's or ectopic ACTH secreting tumour?
Nethaji C, Powell M., Baldeweg SE (London)**

A 31 yrs old woman presented with hirsutism, worsening acne, oligomenorrhoea. There is no past medical history of depression, obesity, or heavy alcohol intake. On examination there was evidence of hirsutism, florid acne, thinning of skin and proximal muscle weakness. Initial investigations showed a raised urinary free cortisol, non-suppression of cortisol after 1mg of dexamethasone overnight, no hypokalaemia and normal anterior pituitary functions. A human CRH test showed an 80% increment in cortisol response. MRI showed a 4 mm lesion of the anterior pituitary. CT scan showed bilateral bulky adrenals, with no lesions in her chest. She underwent transsphenoidal surgery, which failed to lower her cortisol levels. Histology showed normal pituitary tissue. Repeat 24 hour urinary free cortisol levels were raised though Dexamethasone showed good suppression of the cortisol levels. IPSS with human CRH showed no significant gradient between periphery and IPS. Has she cycled out, or have we treated her Cushings, or is there a missing ACTH secreting tumour?

**17. Aggressive Cushing's disease with cavernous sinus involvement – what to do next?
Grageber J, Burnett NG, Pickard JD, Simpson H, Morris DG & Gurnell M (Ipswich and Cambridge)**

In 2005, a 54-year-old man with a 5-year history of diabetes mellitus developed worsening of glycaemic control, hypokalaemia, proximal muscle weakness and emotional lability. Investigations were consistent with Cushing's disease (24hr UFC - 5137nmol/day, ACTH 142ng/L, right sided pituitary macroadenoma with cavernous sinus extension on MRI). Unfortunately, whilst awaiting further investigations he developed staphylococcus aureus septicaemia, and a right atrial thrombus requiring ITU treatment. In September 2005, 6 months after diagnosis he was finally underwent transsphenoidal surgery. Histology confirmed a corticotroph adenoma, but also revealed sphenoidal sinus aspergillosis. Post-operative cortisol levels were consistent with residual Cushing's syndrome, and his postoperative course was complicated by a SFA pseudoaneurysm, secondary to staphylococcus aureus endocarditis.

Ongoing hypercortisolaemia was fortunately controlled by the triazole antifungal agent Voriconazole prescribed for the aspergillosis. Discontinuation of this in June 2006 resulted in clinical and biochemical recurrence of the Cushing's syndrome. Adrenolytic therapy with Metyrapone was initiated, and repeat

imaging confirmed enlargement of the residual pituitary adenoma. Pituitary radiotherapy (55Gy) was commenced in July 2006. This was associated with an acute right third cranial nerve palsy which resolved with high dose steroids. In January 2007 MRI imaging showed reduction in the size of the pituitary lesion, and biochemical control of the Cushing's syndrome was being achieved on a reducing block and replace regime. However, in October 2007 the patient developed a persistent headache and recurrence of the right third cranial nerve palsy. Re-growth of the pituitary adenoma was confirmed, as were rising ACTH levels and hypercortisolaemia. What are the options for ongoing management of the Cushing's disease in this man? Is further surgery including the cavernous sinus a potential course of action?