# THE 6th NATIONAL CLINICOPATHOLOGICAL CONFERENCE ON PITUITARY DISEASE

## Royal College of Physicians, Wednesday 4th February 2004

## Programme

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|---|---|---|
| 9.30 | **Welcome** | Mr Michael Powell (London) |
| 9.40 | **Keynote Lecture**<br>The Natural History of Hypopituitarism | Professor Richard Clayton (Stoke-on-Trent) |
| 10.20 | **Coffee** | |
| 10.40 | **Pituitary Workshop 1**<br>*Chair: Dr Mark Vanderpump (London) and Mr Michael Powell (London)* | |
| | **Open Case Presentations 1**<br>Cases will be presented at approximately ten to fifteen-minute intervals | |

| Panel: | | |
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| | Professor Ashley Grossman | Endocrinology, London |
| | Professor Richard Clayton | Endocrinology, Stoke-on-Trent |
| | Professor Mike Sheppard | Endocrinology, Birmingham |
| | Professor John Monson | Endocrinology, London |
| | Dr James Ahlquist | Endocrinology, Southend |
| | Dr John Bevan | Endocrinology, Aberdeen |
| | Dr Nick Plowman | Radiotherapy, London |
| | Dr Kathy Pigott | Radiotherapy, London |
| | Dr Michael Brada | Radiotherapy, London |
| | Professor Ed Laws | Neurosurgery, Charlottesville |
| | Professor Paolo Cappiabianca | Neurosurgery, Naples |
| | Professor Nicolas de Tribolet | Neurosurgery, Switzerland |
| | Mr Jonathan Pollock | Neurosurgery, London |
| | Mr John Pickard | Neurosurgery, Cambridge |
| | Professor Francesco Scaravilli | Neuropathology, London |

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| 12.20 | **Pituitary OphthalmPituitary Workshop 1: Open Case Presentations** PLANT - ophth. | |
| 12.50 | **Lunch** | |
| 14.00 | **Keynote Lecture**<br>Endocrine Dilemmas in Pituitary Surgery | Professor Ed Laws (Charlottesville) |
| 14.30 | **Pituitary Workshop 2**<br>*Chair: Dr Gerard Conway (London) and Miss Joan Grieve (London)* | |
| 14.30 | **Pituitary Endoscopy – A Neapolitan Update** | Professor Paolo Cappiabianca (Naples) |
| 15.00 | **Open Case Presentations 2 - Hyperprolactinaemia** | |
| 15.30 | **NICE and Growth Hormone Replacement - Update** | Prof John Monson (London) |
| 15.50 | **The Pituitary Foundation - Update** | Mr Tim Wheadon (Chairman) |
| 16.00 | **Tea** | |
| 16.30 | **Close** | |

**Pituitary Workshop 2**
***Chair: Dr Gerard Conway (London) and Miss Joan Grieve (London)***

**1. Cabergoline can treat dementia and confusion in macroprolactinomas**
***D Morganstein[1], N Mendoza[2] and K Meeran[1],***
***Endocrine Unit, Imperial College Faculty of Medicine[1] and Department of Neurosurgery[2], Charing Cross Hospital, London***

A 66 year old female presented with a one month history of new onset confusion, urinary incontinence and falls. She was alert, but had a mental test score of 1 out of 10.CT scan of the head showed hydrocephalus with a large cystic lesion in the region of the pituitary. Baseline endocrinology showed a prolactin of 398,850 mU/l (NR < 625). Her LH was undetectable with an FSH of 0.4 U/l. Cortisol was satisfactory but she had a TSH of 22 mU/l (0.3-4.2) with a Free Thyroxine of 9.6 pmol/l (9.0-26.0). Her Thyroid peroxidase antibodies were positive and her free Thyroxine subsequently fell below the lower limit of normal suggesting coexisting primary hypothyroidism. MRI scan of the pituitary revealed a large pituitary mass extending into the cavernous sinuses with a cystic element extending into the lateral ventricle. She underwent stereotactic drainage of a large intraventricular cyst without any improvement in her mental state. She was then commenced on cabergoline 500mg twice weekly. Her mental state improved over the subsequent 3 weeks to 8 out of 10, with partial resolution of her hydrocephalus. Her prolactin fell to 3735 mU/l within three weeks. She currently continues on cabergoline.
We would welcome the panel's comments on the following points:
1. Indications for surgery in large prolactinomas
2. How long a trial of dopamine agonist therapy
3. Potential effects of cabergoline on mental state.

**2. Macroprolactinaemia: not always an innocent cause of elevated serum prolactin.**

***J AO Ahlquist and MN Fahie Wilson***
***Endocrine Unit & Clinical Biochemistry, Southend Hospital, Westcliff on Sea, Essex.***

Macroprolactin is a naturally occurring high molecular weight form of prolactin, which commonly causes hyperprolactinaemia. As the macroprolactin usually has little or no biological activity, patients with hyperprolactinaemia due to macroprolactin do not normally require treatment. A 24-year-old man presented with a 2-3 year history of breast swelling and galactorrhoea. Sexual function was normal, and there were no visual symptoms. Serum prolactin was elevated at 3865mU/l, and routine macroprolactin screening was positive. Gel filtration chromatography showed that macroprolactin was a minor component (around 30%) of his total prolactin level, with the majority of his excess prolactin being of normal molecular weight. Further investigation revealed a pituitary adenoma in the fossa and extending inferiorly towards the sphenoid sinus. A diagnosis of prolactinoma and co-incidental macroprolactinaemia was made. He was treated with bromocriptine, the galactorrhoea settled but there has been no change in his gynaecomastia; his serum PRL fell to 111mU/l with treatment, and a repeat pituitary MRI after 7 months has showed no change in the tumour size. This case demonstrates the value of quantitative measurement of macroprolactin in the proper assessment of patients with hyperprolactinaemia and macroprolactin.

**3. Prolactinoma in the presence of Schizophrenia**
***D Morganstein[1], N Mendoza[2] and K Meeran[1],***
***Endocrine Unit, Imperial College Faculty of Medicine[1] and Department of Neurosurgery[2], Charing Cross Hospital, London***

A 32-year-old male originally from Nigeria but resident in the UK for the last six years had a history of schizophrenia for 12 years treated with Olanzapine. In June 2003 he had a generalised tonic clonic seizure and was commenced on Phenytoin, having a second seizure in December 2003. He also complained of a 3-month history of lethargy. At this time a CT Head was performed which showed a pituitary lesion together with a parietal lobe lesion thought to represent haemorrhage from a head injury sustained at the time of the seizure. MRI scan showed a large cystic pituitary adenoma distorting the optic chiasm but with no extension outside of the pituitary fossa. His prolactin was elevated at 78,438mU/l (NR <625) LH of 2.3U/l and FSH 2.4U/l. Free thyroxine was 9.9pmol/l (9.0-26.0) with a TSH of 2.80mU/l (0.3-4.2). A short synacthen test performed with 250mg synacthen revealed an undetectable cortisol at time 0 rising to 208nmol/l at 30 minutes and 326nmol/l at 60 minutes.
He was commenced on hydrocortisone replacement and after careful liaison with the psychiatry department his olanzapine was changed to quetiapine and he was commenced on cabergoline 500 mg once weekly. His mental state will be closely monitored on this regime for signs of recurrence of his psychotic symptoms induced by the dopamine agonist.
We would welcome the opinions of the panel regarding the further management of this patient, in particular concerning the combined use of dopamine agonists with antipsychotics, and the role for surgery.

**3. Pituitary apoplexy in an invasive macroprolactinoma during dopamine agonist therapy: management dilemmas.**

***C. Daousi* and I.A. MacFarlane****

****Diabetes & Endocrinology Clinical Research Group, Clinical Sciences Centre, University Hospital Aintree, Lower Lane, Liverpool L9 7AL.***

A 58-year-old male patient was found in 1999 to have a right visual field defect on routine testing by an optician. A referral to an ophthalmologist was made who diagnosed a partial right homonymous hemianopia and arranged an MRI scan of the pituitary which showed a pituitary macroadenoma compressing the optic chiasm, extending out of the suprasellar cistern and into the 3rd ventricle, and also extending laterally into the cavernous sinuses mainly on the left. Baseline pituitary function tests revealed a raised prolactin (61,000 mU/L), TSH 1.11 mU/L, FT4 16.4 pmol/L, IGF-1 18 mmol/l, random cortisol 527 mmol/l, testosterone 8.6 mmol/l, FSH 2.2 and LH 1.2. He was commenced on bromocriptine initially 1.25 mg increased after a week to 2.5 mg OD. Six months later visual fields had improved, a repeat MRI scan showed reduction in the size of the macroadenoma, but prolactin remained raised, therefore his bromocriptine was gradually increased to 5 mg BD.

Two months later he presented with a few days history of headaches, drowsiness and confusion. An urgent CT-scan of his brain showed evidence of fresh haemorrhage in the pituitary with accompanying hydrocephalus. An emergency decompression was performed with insertion of an external ventricular drain. This was followed by a very stormy course on ITU complicated by the need to re-explore the pituitary and reinsert the drain because of CSF leak, pseudomonas and MRSA pneumonia, massive intestinal bleeding and very slow and difficult ventilatory wean. He was eventually discharged from ITU two months later.

Follow up MRI scans showed that the size of the adenoma had remained stable, his visual fields were unchanged and his prolactin level was 29,150 mU/L off bromocriptine. He was reluctant to restart bromocriptine as he felt this may have led to the life threatening apoplexy. He was referred for radiotherapy, which he completed in August 2001. A repeat MRI scan in May 2003 showed a possible slight increase in the size of the adenoma compared to previous scans, his prolactin level was 23,000 mU/L and repeat visual field testing in October 2003 showed a possible small change in the right eye.

What would be the appropriate treatment at this stage? Re-introduction of dopamine agonists despite the previous episode of pituitary apoplexy? Re-operation? Stereotactic radio surgery? We would welcome the views of the panel regarding the optimal management of this patient's recurrent macroprolactinoma.

**4. Difficulties in Diagnosing Acromegaly in Patients with Diabetes mellitus**

***T Brothwood and P-M Bouloux***

***Department of Endocrinology, Royal Free Hospital, London***

A 70-year-old retired Maintenance Fitter was referred in November 1999 with type 2 diabetes, hypertension and bilateral carpal tunnel syndrome. Medication included Glucobay 50mg bd, Gliclazide 240mg/day, Felodipine 10mg/day and Terbinafine 250mg/day. Phenotypically he was acromegaloid with enlarged hands and feet. Shoe Size had increased from 9-11 over past 10 years. He denied sweating excessively. There was no prominence of supra orbital ridges or prognathism. Visual fields were normal. Bilateral lower limb oedema was present. Other findings included height 184cm, weight 104.5Kg BMI 31Kg/$m^2$ and BP 150/90. Biochemical findings included HbA1c 8.9%, Raised GH Levels (OGTT glucose 11.4 – 17.6mmol/l (at 2hours); GH (9.2 – 3.7_g/l). Thyroid and Anterior Pituitary function were normal. He had normal age/sex IGF-1 at 51.5 nmol/l (12.1 –59.8). No focal lesion was seen on MRI scan

Metformin was added and at review in 2001 HbA1c was 7.3% and BP 164/85. The IGF-1 was 45.9 nmol/l. Following clamped glucose levels (4-8 mmol/l) with dextrose infusion and sliding scale insulin, GH detectable throughout (Glu 6.8 – 6.2mmol/l, GH 7.1 -9.8 _g/l). The mean GH was 10.1_g/l during a Growth Hormone Day Curve. A MRI scan now suggested right an anterior pituitary lesion. In Jan 2002 at transsphenoidal surgery a necrotic tumour was removed from right side of pituitary gland. Histology was consistent with a GH adenoma. Post operatively, GH levels 2 _g/l (mean) during an OGTT (Glu 8.1–14.3mmol/l; GH 10.5–0.68_g/l), IGF-1 normalised to 21.1nmol/l at 6-week check. How should patients with type 2 diabetes be investigated for acromegaly?

**5. Management of Pituitary Adenomas in Pregnancy**

***D Morganstein[1], N Mendoza[2] and K Meeran[1],***
***1.Endocrine Unit, Imperial College Faculty of Medicine, Charing Cross Hospital, London, UK***
***2. Department of Neurosurgery, Charing Cross Hospital, London.***

A 25-year-old female presented with several years secondary amenorrhoea and found to have a raised prolactin of 1300 mU/l (NR <625). MRI showed a 1.3cm macroadenoma close to the optic chiasm. Formal visual fields were normal. In view of the unlikely possibility of a prolactinoma she was commenced on Bromocriptine and was then found to be pregnant within two weeks (without having a single menstrual period) and bromocriptine therapy was withdrawn. At 11 weeks gestation she represented with severe headache and postural hypotension. She had an undetectable serum cortisol. Prolactin at this time was 857 mU/l, gonadotrophins were low and she had a free Thyroxine of 12.4 pmol/l (9.0-26.0) with a TSH of 1.10 mU/l (0.3-4.2). Visual fields remained normal and fetal ultrasonography was normal. She was commenced on hydrocortisone replacement therapy. It was thought that she may have had a pituitary apoplexy and after discussion with radiology colleagues a CT scan was performed which showed no haemorrhage in the region of the pituitary fossa. MRI scanning was repeated at 13 weeks pregnancy, which showed a degree of tumour expansion. She continues to have daily headaches however her visual fields by perimetry remain normal and she is only on hydrocortisone replacement and analgesia.

We would be grateful for the panel's views on the following points:
1. Optimum imaging modalities in early pregnancy: should she have an MRI or a pituitary CT or nothing?
2. Management of non-functioning macroadenomas in early pregnancy

**6. A young girl with pituitary stalk pathology.**

***K. Darzy, L. Hoy and AB Grossman.***
***Department of Endocrinology, St. Bartholomew's Hospital, London.***

A girl aged 14 years was diagnosed with cranial diabetes insipidus with a normal MRI scan, except for the loss of the bright signal of the posterior pituitary. She subsequently developed panhypopituitarism and she was on full replacement therapy within 2 years. MRI then demonstrated thickened pituitary stalk and chiasma, which progressed over 12 months. PET scan was negative. Tumour markers were normal except for a slightly elevated HCG in the CSF. Germinoma and optic nerve glioma / pilocytic astrocytoma were the most likely differential diagnoses. A trial of chemotherapy resulted in complete resolution of the suprasellar lesion following the first 2 cycles. Such a dramatic response suggests a diagnosis of germinoma.

**7. Diabetes Insipidus associated with panhypopituitarism and normal imaging – a cause for alarm or a case for reassurance?**

***CH Courtney and SJ Hunter***
***Regional Centre for Endocrinology & Diabetes, Royal Victoria Hospital, Belfast***

A 20-year-old male presented with an acute history of severe thirst and polyuria. He had previously been well and was otherwise asymptomatic with a normal clinical examination including absence of features of hypopituitarism. Plasma sodium was 150 mmol/l (normal 135-145 mmol/l), serum osmolality 309 mosm/kg (285-295 mosm/kg) and urine osmolality 165 mosm/kg. A water deprivation test confirmed evidence of CDI with a rise in urine osmolality from 118 to 577 mosm/kg after 2mcg subcutaneous DDAVP. Serum vasopressin was unmeasurable. Treatment with desmospray produced a rapid resolution of his symptoms. Gadolinium-enhanced MRI scan of pituitary fossa showed loss of the posterior pituitary bright spot but no other abnormalities were identified and a CXR was normal. Assessment of anterior pituitary function revealed panhypopituitarism: serum testosterone <0.7 nmol/l (normal 12-30 nmol/l) with unmeasurable gonadotrophins, prolactin 1370 mU/l (normal <350 mU/l), free thyroxine 7.7 pmol/l (normal 7.6-19.7 pmol/l), TSH 1.35 mU/L (normal 0.45-4.5 mU/l). During an ITT the peak serum cortisol was 42 nmol/l (normal > 550 nmol/l) and peak GH 2.7 mU/l (normal >20 mU/). He was commenced on replacement glucocorticoid therapy, thyroxine and sustanon. Despite appropriate replacement therapy, he complained of increasing fatigue and six months later was also commenced on GH replacement. At 9 months he reported blurred vision and was found to have reduced visual acuity, a right-sided homonymous hemianopia and bilateral internuclear ophthalmoplegia. An MRI scan at this time showed enhancing, high signal material in the periventricular regions surrounding the lateral ventricles, the hypothalamus, the optic pathways and the pons. Ependymal biopsy showed poorly differentiated carcinoma cells. No primary tumour was identified and he was subsequently transferred to the oncology department for cranial radiotherapy.
Idiopathic CDI is the most common aetiological diagnosis in approximately 50% of patients. Although abnormalities of anterior pituitary function can occur in idiopathic CDI in this case the presence of panhypopituitarism suggested an alternate diagnosis. The later association of pituitary dysfunction with brain stem abnormalities and bilateral INO is also unusual. This case illustrates the importance of careful clinical follow-up before a diagnosis of idiopathic CDI is made.

**8. Pituitary tumours in patients with MEN-1 are more aggressive than in patients with sporadic tumours**

***WS Dhillo, K Meeran and JF Todd***
***Endocrine Unit, Imperial College Faculty of Medicine, Hammersmith Hospital, London***

A 16-year-old female was initially referred to her local hospital in 1996 with right loin pain and vomiting. She was hypercalcaemic with a low serum phosphate and elevated serum parathyroid hormone level consistent with primary hyperparathyroidism. An abdominal USS revealed renal calculi. On direct questioning, there was a 3-year history of weight gain with cessation of linear growth and primary amennorrhoea. Her father had MEN-1. On examination, she was Cushingoid with a proximal myopathy and BP145/95. She was below the 3rd and above the 90th centile for height and weight respectively.

Initial investigations revealed elevated 24h urinary free cortisols (UFC) with failure to suppress on low dose dexamethasone suppression test (LDDST). Pituitary MRI showed 1cm left-sided pituitary adenoma and she underwent transsphenoidal hypophysectomy (TPSH) in February 1997. Post-operatively, she remained Cushingoid and inferior petrosal sinus sampling (IPSS) suggested the presence of left sided pituitary lesion. Repeat TPSH was performed. However, she was again not cured and was commenced on ketoconazole 200mg od following which she achieved menarche. In July 2001 she underwent parathyroidectomy during which 2 hyperplastic parathyroid glands were removed. In January 2003, her care was transferred to our hospital. LDDST showed inadequate of suppression of cortisol levels (t=0 cortisol 506nmol/l, $t_{=48}$ cortisol 275 nmol/l) although she demonstrated > 80% suppression on a high dose dexamethasone suppression test (HDDST) (t=0 cortisol 649nmol/l, t=48 cortisol 84nmol/l). MRI pituitary showed some residual right-sided tissue. Repeat IPSS suggested a right-sided pituitary lesion with central inferior petrosal sinus to peripheral ACTH gradient of 16 following CRH injection. We discussed her case with our neurosurgeon. Since the patient had already had two failed TPSHs previously and hoped for future fertility, we decided to offer the patient endoscopic bilateral adrenalectomy. Post-operatively her ACTH was 86 ng/L. However, despite adequate hydrocortisone replacement within 4 months the patient was noted to have hyperpigmentation and an elevated ACTH 1300ng/L. Repeat MRI showed a small expansion of the pituitary tissue consistent with Nelson's syndrome. She underwent a further TPSH. The histology confirmed an ACTH secreting adenoma and her postoperative ACTH is 26 ng/L.

In summary this lady with probable MEN-1, primary hyperparathyroidism and recurrent Cushing's disease developed Nelson's syndrome 4 months after bilateral adrenalectomy. Nelson's syndrome is rare in the first year post-adrenalectomy with the mean incidence at 4.5-6.5 years post-surgery. Patients with MEN-1 and pituitary disease have larger, more aggressive tumours than patients with sporadic tumours (macroadenomas occur in 85% MEN-1 patients vs 42% sporadic cases and 50% patients with MEN-1 had ACTH secreting macroadenomas vs.10% sporadic cases)[1]. This case highlights that the risk of Nelson's syndrome may be higher in patients with MEN-1. The panels thoughts on whether patients with MEN-1 and Cushing's disease should be offered pituitary surgery over bilateral adrenalectomy in the event of recurrent disease would be very interesting and helpful in the future management of these patients.

(1) Verges B et al. JCEM 87:457-465, 2002

**9. Growth hormone excess in a child with neurofibromatosis type 1 (NF1) and diffuse low-grade glioma.**

***N Hopper, A Albanese***
***Department of Paediatrics, Royal Marsden Hospital, Surrey***

We present a 7-year-old girl with (NF-1) and a diffuse suprasellar low-grade glioma that suffered from obesity and tall stature. Growth hormone hypersecretion was documented prior and after the completion of her chemotherapy treatment. Baseline IGF-1 and IGFBP-3 levels were elevated, a daytime GH profile was abnormal and 2 oral glucose tolerance tests failed to produce suppression of GH levels. No other endocrinopathies were present and she was prepubertal. MRI revealed a low-grade glioma involving the brain stem, basal ganglia, cerebellum and optic pathway but a normal pituitary gland. Octreotide administration produced suppression of GH levels and the patient was commenced on treatment with Sandostatin LAR.

Gigantism and GH excess are exceedingly rare in children and usually due to a pituitary adenoma. GH excess in NF-1 with gliomata not directly affecting the pituitary has been described and is thought to be most likely due to interruption of somatostatin tone.

**Pituitary Workshop 1: Open Case Presentations**
***Chair: Dr Mark Vanderpump (London) and Mr Michael Powell (London)***

**1. Aggressive recurrence in semi silent corticotroph after one craniotoy, six transsphenoidal procedures, adrenalectomy, radiotherapy and gamma knife.**
***Cudlip S,. Powell M, Conway G***

This 39 year old lady has been presented at each of the proceding CPC's! She initially presented aged 18 as a giant Cushings tumour and underwent a craniotomy and appeared 'cured'. Her tumour recurred with visual syptoms as a silent corticotroph about 10 years later during the post partum phase from her first child. Further surgery followed by radiotherapy followed but the tumour recurred and she was sent for transsphenoidal resection to Sheffield augmented with photodynamic therapy. This was unsuccessful and she underwent a third procedure later that year here. She underwent a further procedure in 2000 followed by Gamma Knife to a recurrence in the right lateral border of the fossa. By this stage she was complaining of Cushing's symptoms, coincidental to her tumour recurrence. Each time we resected, these symptoms improved. A further attempt at getting at a major regrowth now in the cavernous sinus merely rendered her panhypopit and with DI, but a midface approach in 2002 substantially improved her.

Last summer, with a satisfactory scan, as her Cushing's symptoms were becoming very troublesome, she underwent adrenalectomy.

Although significantly better, she now has cavernous sinus symptoms from a significant cavernous recurrence.

**2. An Unexpected Finding**
***Mitchell CS, Antoun N, Pickard VKK & Gurnell M***
***Addenbrooke's Hospital, Cambridge***

A previously fit and well 34-year-old woman presented to the gynaecology clinic with a 12-month history of galactorrhoea and secondary amenorrhoea. She was found to have an elevated prolactin level (1800mU/l) together with evidence of central hypogonadism and growth hormone (GH) deficiency (peak GH 4.0mU/l during an ITT), but with normal thyroid function and adrenal reserve. A CT scan of the pituitary fossa revealed appearances suggestive of a pituitary tumour with minimal suprasellar extension. The patient was treated with bromocriptine with complete resolution of her symptoms. However, serial CT scans suggested progressive tumour enlargement and, 6 years after her initial presentation, she underwent sub-frontal excision of the lesion with histology consistent with a non-functioning pituitary adenoma. Post-operatively, she underwent conventional external DXT (45Gy) and developed panhypopituitarism. Over the next decade, serial MRI imaging showed a partially empty sella with no recurrence and the patient remained well. However, sixteen years after surgery/DXT, and in the absence of symptoms, a routine surveillance MRI scan unexpectedly revealed extensive tumour regrowth and the patient is currently awaiting further neurosurgical intervention by the transsphenoidal approach. Whilst such late recurrence is relatively unusual, especially when adjunctive DXT has been given, this case serves to emphasize the need for continued vigilance, and raises the important question of whether it can ever be considered safe to discontinue radiological follow-up?