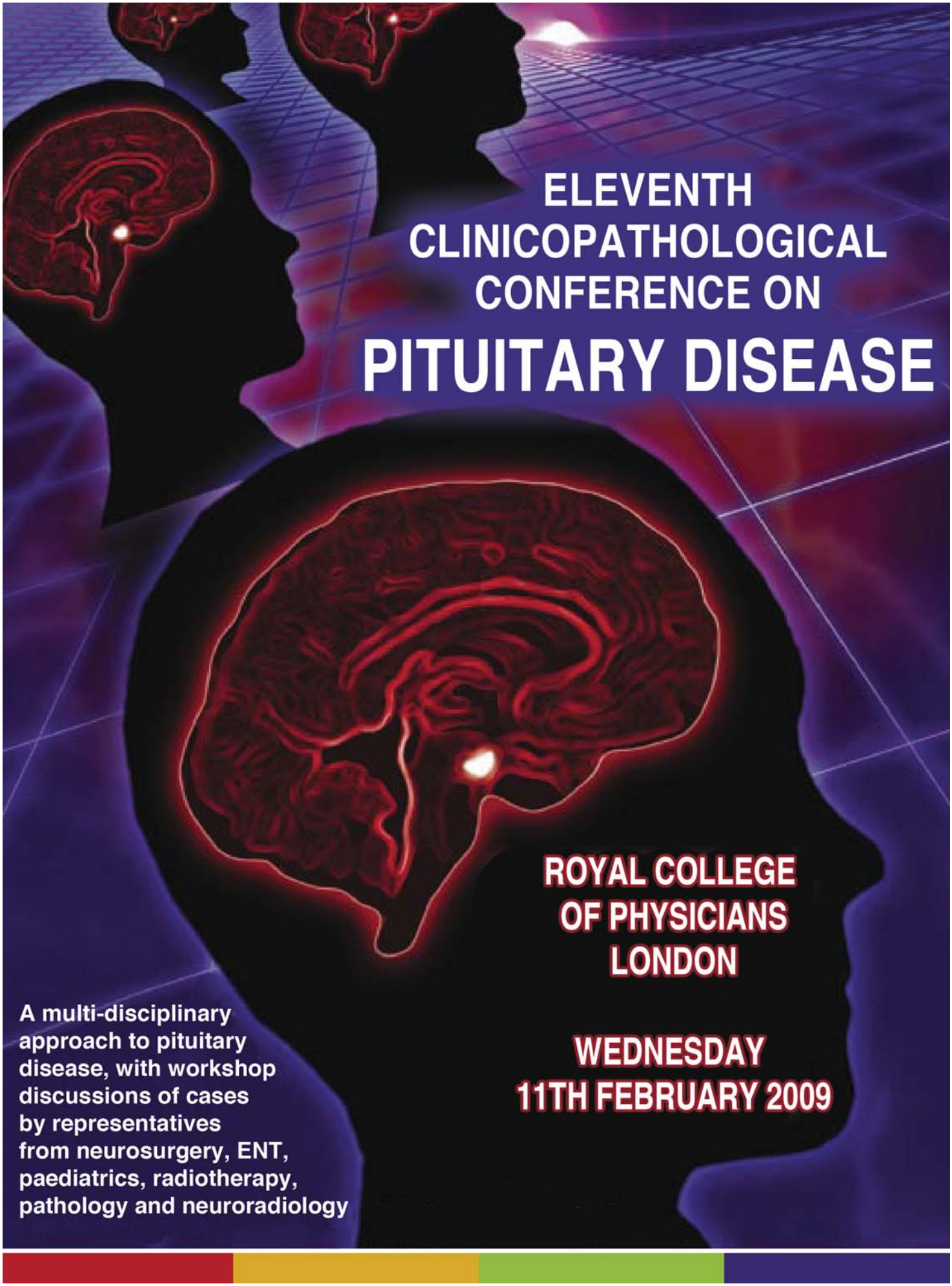


Date of Preparation: SAI08 - 0096 December 2008

Sponsored by an educational grant from Merck Serono

MERCK SERONO

Forum 1

A variety of pituitary cases

Chairs: Dr Mark Vanderpump, Mr Michael Powell, London

1. Cyclical Cushing's syndrome due to ectopic Adrenocorticotrophic Hormone secretion by a bronchial carcinoid

Senthil Rajasekaran, Niki Karavitaki, John A.H. Wass (Oxford)

Introduction

Cyclical Cushing's syndrome(CS), was first described in 1971 by Bailey in a patient with bronchial carcinoid.The Diagnosis of Cyclical CS is often very difficult resulting in delayed treatment. In a series of 65 patients with cyclical CS, Cushing's disease was the underlying cause in 54%, ectopic CS in 26% and primary adrenal pathology in 11%. We report a rare case of cyclical CS due to bronchial carcinoid and discuss the diagnostic difficulties encountered.

Case history

A 42 yr old lady presented with weight gain, hirsutism, thin skin and easy bruising. She was also diagnosed with Type2 Diabetes Mellitus Hypertension and Hypokalemia. She was commenced on Metformin, Ramipril and Spirinolactone. She had all the classical features of CS. Her initial hormonal assessment confirmed ACTH dependent CS. She then underwent further differential diagnostic work-up on a number of occasions (shown in table), as her 24 hour urine free cortisol levels were suggesting Cyclical CS.

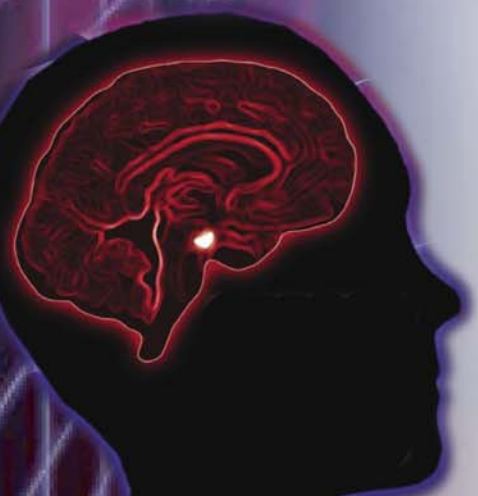
	10/06	10/06	04/07	06/07	10/07	11/07	12/07	04/08
24hr urinary free cortisol (0-560 nmol/24)	451	93	4887	165	1704	637	794	1878
Midnight serum cortisol (nmol/L)	219	215	857					
LDDST (serum cortisol 48hrs)	95		908					
HDDST (serum cortisol 48hrs)	264		258					
CRH test % incerase	ACTH: 60% Cortisol:	40%	ACTH: 30% Cortisol:	5%				
Serum K (mmol/L)	3.5		2.1	3.0	3.0	3.5	3.4	2.5
IPSS	no gradient			no gradient	no gradient			
MRI Pituitary	normal		normal					

After the 3rd IPSS study, she had a CT scan of her chest which disclosed a 8 mm nodule at the left pulmonary base. Whole body PET scan showed increased uptake by the pulmonary nodule. Chromogranins and 24hrs urinary 5HIAA levels were normal. She then underwent left thoracotomy and resection of the pulmonary nodule and subcarinal nodes. Histology showed atypical carcinoid tumour with metastatic deposit in one of the five subcarinal nodes.

Post operatively, she was biochemically cured and there was no radiological evidence of residual disease. However, the last Cushing's work-up 8 months after the surgery did not exclude completely the presence of active CS. In view of this equivocal result we have organized further radiological investigations.

Discussion

This case illustrates the difficulties we are likely to encounter in patients with cyclical CS, which make the diagnosis of patients with ectopic CS even more challenging. The optimal diagnostic and therapeutic approach for such patients will be discussed.



2. A family with early-onset growth hormone and prolactin-secreting pituitary tumours
Turner L, Robertson I, Barwell J, Greening J, Levy MJ, Howlett TA (Leicester, Nottingham)

We present a 7 year old girl (Case A) who experienced sudden onset of severe headache and right-sided third nerve palsy. Prior to acute admission, she had been referred to the paediatric endocrinologists because of a several month history of accelerated growth (> 99th centile for height) and new onset headache. Her initial CT scan in casualty showed a mass in the pituitary fossa with invasion of the right cavernous sinus. Preliminary endocrine investigation showed an elevated IGF-1 level with incomplete suppression of growth hormone (GH) after oral glucose tolerance testing. She was transferred to the neurosurgical Unit with a clinical diagnosis of an apoplectic event within a GH-secreting pituitary tumour. A trans-sphenoidal biopsy showed a somatotroph adenoma and she was managed conservatively. A trial of cabergoline was followed by a reduction in IGF-1 and GH levels to below normal the normal range, with suppression of prolactin.
The cabergoline has been discontinued and she is due for dynamic re-assessment of her GH status and re-imaging of the pituitary fossa. Her headache and 3rd nerve palsy have resolved and her growth continues to be monitored closely.
Numerous members of the proband's family are known to our clinic with early onset GH and prolactin-secreting pituitary tumours. A's mother (Case B) presented with a micro-prolactinoma at the age of 15 with primary amenorrhoea and galactorrhoea and was treated with a variety of dopamine agonists and pituitary surgery. B's cousin was diagnosed with acromegaly at the age of 32 years (Case C), having presented with oligomenorrhoea, hyperprolactinaemia, reduced fertility and headache and had subsequent trans-sphenoidal hypophysectomy, radiotherapy and octreotide. C's father grew rapidly at the age of 17 and subsequently developed of classical acromegalic features (Case D). A glucose tolerance test performed in 1973 (at age 31) and again in 1993 showed incomplete suppression of GH, but subsequent GH / IGF-1 levels and pituitary imaging have been normal over the last decade despite no specific treatment. D's brother has been treated elsewhere with a dopamine agonist for prolactinoma and possibly acromegaly. None of the family has hypercalcaemia or pancreatic neoplasia, and gene testing for MEN-1 is negative. Case A and her mother have been seen by our clinical geneticists who have commented on the presence of pigmented skin lesions but there is no evidence of Cushing syndrome or cardiac myxomas in the family.

This family appear to have a rare pedigree presenting exclusively with GH and prolactin-secreting pituitary tumours. Given the very young age of presentation of the proband, the possibility of genetic anticipation is raised. We would be interested to hear the views of the audience about the unifying diagnosis, and whether further genetic analysis might lead to new insights into the hypothalamic control of the GH / prolactin axes.

3. Macroprolactinoma and Cushing's Disease: An Unusual Combination with Initial Treatment Response to Dopamine Agonist Therapy: What next?
Nagi D, Azzan R, Jenkins R (Wakefield)

Secretion of multiple pituitary hormones by pituitary adenomas is relatively rare. It is usually due to a single tumour producing more than one hormone. Two distinct a denomas secreting different hormones have been described (1), but this is uncommon. It has also been documented that the hormonal production of a particular tumour may change with time, therefore behaving like a tumour secreting multiple hormones but not simultaneously (2,3).
The commonest combination of hormone secretion is growth hormone (GH) and prolactin (PRL) but the combined secretion of GH/thyroid stimulating hormone (TSH) and PRL/TSH as well as GH/PRL/TSH, have all been documented (4,5). The combination of adrenocorti-cotrophic hormone (ACTH)/PRL is very rare indeed, with only a few cases reported to date (2, 6-9).

History and examination
An 18 year old young man was first seen in the ENT department with bilateral swelling of the supraclavicular fossae. A clinical diagnosis of Cushing's syndrome was made and the patient was referred to the Endocrine team. His past medical history is unremarkable and he was not on any regular medications. On examination he was grossly Cushingoid with typical facial features (Fig. 1A), abdominal striae, proximal muscle weakness and elevated blood pressure at 150/100. His visual field testing in clinic suggested a mild bitemporal hemianopia.

Investigations
Renal function and electrolytes were normal. Thyroid function tests showed a low fT4 at 8.7 pmol/L with a TSH of 0.69 mIU/L. Prolactin was 68280 mIU/ml and 24-hr urinary free cortisol (UFC) was 3860 nmol/24 hr. Random cortisol was 985 nmol/L with an ACTH of 104 ng/L. Testosterone was 13.5 nmol/L, SHBG 6 nmol/L, FSH 4.4 IU/L and LH 6.7 IU/L. The results of a cortisol day curve are shown in Table 1A. A high dose dexamethasone suppression test showed a basal cortisol of 809 nmol/L suppressing to 247 nmol/L, indicating Cushing's disease. An MRI showed a large pituitary mass with minimal suprasellar extension and very little normal pituitary tissue and this is shown in Fig. 2A.

Management
The patient was commenced on bromocriptine but developed skin rash and arthralgia and was therefore switched to cabergoline 500 mcg twice weekly. Four weeks later, he was admitted for a cortisol day curve as a baseline for commencing metyrapone therapy for his Cushing's disease. During his admission, it was noted that the patient's physical appearance had improved dramatically (Fig. 1B). Clinically, it was felt that his Cushing's disease has remitted, and his BP normalised to 105/60 with no postural hypotension. The clinical suspicion of disease remission was confirmed by a cortisol day curve (Table 2B). His repeat endocrine tests showed a prolactin of 1801 mIU/L, testosterone 28.3 nmol/L, SHBG 70 nmol/L, FSH 2.9 IU/L, LH 5.2 IU/L, fT4 9.2 pmol/L and TSH 2.55 mIU/L. His UFC was less than 36 nmol/24 hr. Repeat MRI performed 6 weeks after starting cabergoline treatment showed 30% reduction in the volume of the pituitary tumour (Fig. 2B).

Follllow up
The patient has been under follow up for 28 months now. He remains on cabergoline and his Cushing's disease has remained in complete remission. Fig. 1C and Fig. 1D show the patient at 7 months and 28 months post treatment. The response to cabergoline treatment was quick and impressive with almost complete shut down in cortisol production. Our patient was indeed hypoadrenal on repeat cortisol day curve and was treated with hydrocortisone replacement therapy for few months. We anticipated that with time he would resume normal cortisol production, which had been the case (data not shown) and his hydrocortisone treatment was subsequently discontinued.
Repeat MRI showed 30% reduction in the volume of the pituitary tumour.. The case is unusual in that a single pituitary tumour would appear to be responsible for prolactin as well as ACTH secretion. The patient had a dramatic response to Cabergoline therapy with resolution of his symptoms and shrinkage of the pituitary tumour. This patients now has been on Cabergoline treatment with complete remission of Cushing's Syndrome and normalisation of Prolactin levels, for 6 years. We would like to discuss the future option for management of this young man.

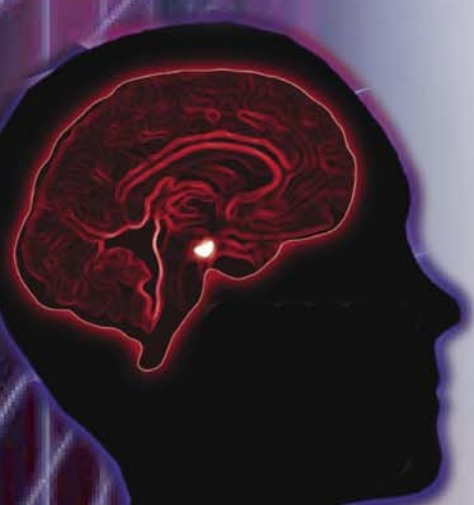
4. Pregnancy, prolactin and an expanding problem!
Bhake R, Barnfield S, Trinder J and Bradley KJ (Bristol)

A 23 year old lady, who had moved to the UK from Poland 2 years previously, was referred by her GP to the endocrine service at the Bristol Royal Infirmary in March 2008.
Her original presentation had been with a six month history of amenorrhoea at the age of 19 years. The details of her investigations in Poland were unavailable to us but she was able to tell us that she had been treated fairly consistently with bromocriptine, obtaining renewed prescriptions during her visits to Poland. At the point of referral she had experienced four months of amenorrhoea having run out of her dopamine agonist therapy and her GP had appropriately refused to provide an ongoing prescription without further clarity regarding the diagnosis. Her clinical examination was entirely normal and her anterior pituitary profile was unremarkable apart from a significantly elevated prolactin at 68,306 mIU/L, which was consistent with the diagnosis of a macroprolactinoma.
On direct questioning she expressed a wish to start a family within the near future and we advised her carefully about the need for adequate contraception in order to postpone conception for a number of months until such a time that we had gained biochemical and radiological control of the tumour. She concurred with this plan and consequently cabergoline was commenced immediately which rapidly restored her menstrual cycle and the drug was titrated up every two weeks to a final dose of 500mcg twice per week. Although she had tolerated bromocriptine reasonably well over the previous four years she had experienced some side-effects and hence we opted for cabergoline therapy. Formal visual field testing was normal but an urgent MRI of the pituitary gland showed a substantial pituitary mass of 20x16mm (9mm clear of the chiasm), confirming the diagnosis of a macroprolactinoma.
When she was reassessed in May 2008 she was asymptomatic and her prolactin had fallen to 3,300mIU/L. A further prolactin level and a repeat MRI were planned for June, three months post initiation of dopamine agonist therapy, to stage her response to treatment. However, the patient informed us in June that she had stopped her cabergoline two weeks previously at the end of May as she had missed a period and that her home pregnancy test was positive. As we had achieved a significant biochemical response after three months of treatment, we decided to urgently assess the radiological response and to hold off further dopamine agonist therapy pending this result. If there was evidence of significant residual tumour then we planned to introduce and maintain her on bromocriptine throughout the pregnancy whilst if there was evidence of successful tumour shrinkage then we planned on careful clinical and visual field monitoring. She was advised to look out for symptoms indicative of an enlarging adenoma and to contact us immediately if they developed. The planned repeat MRI examination was expedited to urgent and visual field assessments were booked for each trimester.
We managed her ongoing care in our maternal medicine endocrine clinic and she had her initial assessment within a week of informing us that she was pregnant. However, there was a break in communication in the ensuing weeks as she was successively unable to attend two clinic appointments, two radiology appointments and a visual field assessment appointment due firstly, to a holiday and then due to work commitments.

We were also unsuccessful in engaging her either by letter or by telephone.
She subsequently attended clinic in October 2008, at 26 weeks gestation, having just had her MRI scan a few days previously. Her motivation for re-attending was significant and unremitting headaches which were present on waking. Her MRI scan revealed dramatic tumour expansion such that it now impinged upon the optic chiasm, encased the right carotid artery, indented the right temporal lobe and had also invaded inferiorly into the sphenoid sinus and eroded infero-laterally into the skull base. Her prolactin was 69,000mIU/L and she was commenced on a rapid titration regimen with bromocriptine, in view of its robust safety data in pregnancy, to reach a dose of 2.5mg bd. Her headaches resolved within a few days and her prolactin fell to 12,600mIU/L after four weeks of treatment. Her visual fields remained normal. A transient increase in her prolactin to 25,900mIU/L was then seen at the same time as she was unable to attend a further clinic appointment but we established on the telephone that she had experienced some nausea and vomiting with the bromocriptine that she felt had been transient and although we debated the switch to cabergoline this was not instituted.
On 21 December 2008 at 33+6 weeks gestation she went into spontaneous labour and delivered a baby boy prematurely with no complications. One day post delivery the obstetricians reassessed her prolactin and found it to be 31,100mIU/L. The baby spent the first few days on NICU but is developing normally given his gestation. We continued her bromocriptine at 2.5mg bd after discussing the risks and benefits and she subsequently successfully established and maintained breast feeding. She remains well and her latest prolactin four weeks after delivery is 5,050mIU/L. A repeat MRI is pending.
The issues and controversies highlighted by this case relate to various aspects of her care:

Timing of agent withdrawal: Should dopamine agonist therapy be withdrawn when pregnancy arises relatively early in the treatment of a macroprolactinoma when the risk of enlargement, although still low, is relatively greater.
Choice of agent: Given recent MHRA reinforcement of the guidance that cabergoline should be stopped at least one month prior to conception, should we strongly encourage women of child bearing age to persist with bromocriptine despite significant side-effects which are impacting upon their everyday life and perhaps influencing compliance? Importantly, prolactinomas may also be less responsive to bromocriptine as opposed to cabergoline.
Fibrotic cardiac valvulopathy: the MHRA safety update was issued in October 2008 and consequently this patient has not yet had cardiac echocardiography. She has no clinical evidence of cardiac compromise and we fear that she may not engage in ongoing therapy if she learns that cardiac valvopathy is a 'very common' side-effect.
Monitoring: How is it clinically appropriate and cost effective to monitor patients with macro (or micro) prolactinomas during pregnancy given the relatively low risk of complications and the current demand on NHS resources? Should formal visual fields be carried out each trimester or will a clinical assessment suffice and is there ever a role for prolactin measurement given the difficulty interpreting the result in the context of pregnancy. Alternatively should patients not be monitored but simply advised to seek help if they develop symptoms? All of these approaches are currently utilised by different endocrine centres in the UK and there is no clearly established consensus.
Imaging: When is it appropriate or essential to request a pituitary MRI in pregnancy given that, although there are no known risks, radiologists ask us to limit use of this technology, especially in the first trimester?
Communication barriers: Significant clinical risk may arise when patients fail to engage fully in their care and how much can this lack of engagement be deemed the responsibility of the health care professional.
Lactation: Should a patient on bromocriptine be encouraged to breast-feed if it is physiologically possible?
Future fertility: Once a patients has had significant enlargement of a prolactinoma during pregnancy how should they be managed prior to and during subsequent pregnancies?

5. Lymphocytic hypophysitis secondary to a ruptured Rathke's cleft cyst: a diagnostic and management challenge
P. Mehta, F. Roncaroli, A. Mehta, M. Bhojak, J. Lawrence, L.R. Bridges, A. Belli, K. Meeran, ECI Hatfield, W.S. Dhillo (London, Salisbury, Edinburgh,Southampton)



We describe a 34-year old female who presented with secondary amenorrhoea and fatigue. There were no features of infection, or autoimmune diseases. Investigations revealed panhypopituitarism and she was prescribed replacement corticosteroids, thyroxine and HRT. She subsequently developed diabetes insipidus and was commenced on desmopressin. MRI scans showed a peripherally enhancing pituitary mass abutting the optic chiasm. The lesion was approached transphenoidally with the aim of taking a diagnostic sample. A follow-up imaging demonstrated re-growth of the lesion 14 months after the initial operation with chiasmal compression. The patient underwent second transphenoidal surgery. Pathological examination of the samples from the first operation showed fragments of Rathke's cleft cyst and adenohypophysis with moderate chronic inflammation. The inflammatory infiltrate was composed mostly of CD8-positive T lymphocytes. No adenoma was present and no micro-organisms were identified.

The sample from the second operation showed granulation tissue associated with a considerable macrophagic infiltrate. These features were consistent with lymphocytic hypophysitis secondary to ruptured Rathke's cleft cyst. An MRI scan performed seven months after the second operation demonstrated further expansion of the cystic lesion. The patient was given a trial of high-dose prednisolone. A repeat MRI to assess response to steroids revealed no change in size of the cyst but reduced contrast enhancement. The patient remains panhypopituitary on replacement therapy.

Given the rarity of the association between Rathke's cleft cyst and hypophysitis, we would like to ask the expert panel how they would optimally manage this patient?

Would further surgery be appropriate?

Should further steroid treatment be given?

Would radiotherapy be advisable?

Forum 2

Management of pituitary apoplexy- Towards a consensus
Chairs: Dr SE Baldeweg (London) and Prof JAH Wass (Oxford)

6. Conservative managment of pituitary apoplexy

R.Fikri R, Johnston C, .Kong C (Hemel Hempstead)

A 55-year-old man who presented with a severe headache, which was sudden, together with photophobia and nausea just 6 days after induction chemotherapy for acute myeloid leukaemia.
On examination he was febrile and had neck stiffness but no focal neurology. He bloods showed that he was thrombocytopenic (platelets 19 $x10^9$ /L), mild coagulopathy and neutropenia (neutrophils 0.5 $x10^9$ /L.CSF examination showed 1 WBC/mm3, 19 RBCs/mm (traumatic tap), no xanthochromia, normal protein and glucose and no organisms were seen on CSF culture.
Unenhanced CT scan of the brain was normal. However, in view of the strong clinical suspicion of intracranial bleeding an MRI was performed which revealed an enlarged pituitary gland with high signal intensities on T1 weighted images, indicating a haemorrhage within the gland likely to be a previously undiagnosed pituitary adenoma. The pituitary was bulging into the suprasellar fossa with no pressure on the optic chiasm. Pituitary function tests showed evidence of hypopituitarism and add on tests from a sample taken 4 days prior to the event showed no evidence of endocrinopathy, which suggests that the adenoma was non-functioning. (which is the commonest associated pituitary tumour) and that the hypopituitarism was acute as a result of pituitary apoplexy. The patient was started on DDAVP, hydrocortisone and testosterone replacement therapy. The headache resolved, fever subsided and the platelet count remained stable at around 50 000 /l. He achieved complete remission of the AML after the first course of treatment and subsequent courses were uneventful. A follow – up MRI showed an almost complete resolution of the pituitary haemorrhage but he remained in hypopituitarism.
Pituitary apoplexy is characterised by headache, meningism, altered mental status, opthalmoplegia or visual loss. It occurs most commonly in patients with previously undiagnosed pituitary adenomas. . Those patients who have a pituitary tumour haemorrhage/haemorrhagic infarction have a more severe clinical picture and worse outcome than those who have a pituitary infarction alone The common precipitating factors are surgery (particularly cardiac), coagulopathy, thrombocytopenia and it has been described after dynamic pituitary testing or hormone stimulation states like pregnancy and HRT. Endocrine recovery is uncommon
Our case demonstrates the importance of proceeding to an MRI scan if the diagnosis is suspected since it is diagnostic in only 30 % of cases despite a presence of a sellar mass in upto 70 %. It also illustrates the instantaneous effect a pituitary apoplexy can have on the pituitary function, hence a high index of suspicion is necessary and prompt treatment may be life saving. Care should be taken when performing surgery, dynamic pituitary testing, giving HRT or anticoagulating patients with a known pituitary adenoma. Finally, it supports the conservative management of this condition, especially if there are neuro-opthalmic complications.

7. Pituitary apoplexy: a challenge for diagnosis and management.

Esther Nemati, James Ahlquist and Michael Powell (Southend and London)

Following a family night out at a Chinese restaurant, a 70 year old man developed diarrhoea and vomiting. Two days later he developed sudden onset headache, which was not severe, mild confusion, double vision, and mild left sided limb weakness.
On presentation, he was febrile and mildly confused. Initially there was a partial right ptosis; over the following three days this progressed to complete right ptosis and partial left ptosis, with complete ophthalmoplegia of the right eye and a left third nerve palsy. He also had mild left sided hemiparesis. A CT scan of his head showed a 20mm pituitary mass which was initially considered to be an incidental finding.

An diagnosis of suspected botulism was made. The Health Protection Agency was contacted, and he was given botulinum antitoxin to which he had an anaphylactic reaction. Endocrine on day 6 assessment demonstrated complete anterior hypopituitarism, and a bitemporal hemianopia. MRI pituitary showed a pituitary mass, 17mm x 38mm, arising from an enlarged fossa and compressing the optic chiasm. CSF examination showed protein 0.96 g/l with a mild lymphocytosis.
He was treated with hydrocortisone, and underwent trans-sphenoidal evacuation of a haemorrhagic pituitary mass seven days after initial presentation. He made a rapid recovery, with full return of higher mental function and gradual resolution of his diplopia and visual field defect. There was no recovery of pituitary function.
This case demonstrates that pituitary apoplexy can be hard to diagnose, and may mimic other acute neurological illnesses. The optimal timing of pituitary surgery is often debated: in this case surgery was not undertaken until seven days after presentation, without obvious harm arising from the delay.

8. Three Perplexing Cases: Controversies in Managing Pituitary Apoplexy
Maruthappu T, Mehta SR, Elgayar H, Wynne K, Mendoza N, Mehta A, Morganstein D, Hatfield E, Tan T and Meeran K (Imperial , London)

Pituitary apoplexy is an uncommon and potentially fatal disorder. Its rarity makes establishing evidence based guidelines difficult. We present 3 cases which have presented in the past year:
Case 1: 30 year old male with no concurrent medical illness, presented with sudden onset severe headache, photophobia and fever. Clinical examination was normal. Meningitis was excluded. MRI revealed a haemorrhagic suprasellar mass with superior displacement of the optic chiasm. Pituitary function showed hypogonadotrophic hypogonadism. 9 am cortisol was 121 nmol/L. This patient was managed conservatively and was successfully discharged on hydrocortisone.
Case 2: a 31 year old lady presented with a 5 day history of severe headache with vomiting. Neurological examination and visual fields were normal. MRI showed evidence of a pituitary macroadenoma abutting but not compressing the optic chiasm, with evidence of haemorrhage. Humphrey's perimetry was normal. Baseline pituitary function tests showed a normal TSH of 0.47 mU/L, free T4 of 11.5 pmol/L (9-26), prolactin of 486 mU/L, IGF-1 of 27.4 nmol/L and cortisol of 367nmol/L. She was discharged on hydrocortisone and is currently awaiting re-evaluation.
Case 3: A 29 year old male attended A&E with a 24 hour history of headache, vomiting and diplopia. On neurological examination he had a right VIth nerve palsy. A CT and MRI confirmed a 2.5cm heterogeneous mass in the pituitary fossa extending into the cavernous sinus and the optic chiasm with evidence of a recent haemorrhage. Perimetry was normal. Baseline pituitary function tests revealed TSH 1.12mU/L, T4 9.9pmol/L, LH 1.8 IU/L, FSH 4.1 IU/L, Prolactin 96 mU/l, Testosterone 8 nmol/L, Cortisol 284nmol/L, Growth Hormone 0.37 ug/l and ACTH 13.4ng/L. He was commenced on Hydrocortisone. Urgent trans-sphenoidal hypophysectomy was performed due to cranial nerve compression and the risk of visual field loss. Histology revealed a necrotic gonadotroph adenoma expressing the ß subunit of FSH. His VIth nerve palsy persists.
These cases highlight the heterogeneous presentations of pituitary apoplexy. Prompt diagnosis is essential to ensure that patients receive appropriate hormone replacement. Controversies remain as to the optimal management, viz.:
What are the benefits of emergency surgery vs treatment with steroids?
What are the indications for surgery?
What are the long term outcomes: recurrence and need for hormonal replacement?

9. Experience of pituitary apoplexy in 58 patients
Pathak A (Sheffield & Chandigarh, India)

Forum 3

All about Cushing's

Chairs: Dr Conway and Mr Powell (London)

10. A silent Corticotroph adenoma leading to aggressive pituitary Cushing's disease
Aung, T, Karavitaki N, Wass JAH(Oxford)

Background: Silent corticotroph adenoma was first described in 1978 by Kovacs. These tumours account for 1.1-6% of surgically removed pituitary adenomas and 17-22% of those with positive ACTH stains. 87-100% is macroadenomas with suprasellar extension and they may show potential aggressive behaviour, particularly upon recurrence.

History: A 62 year old gentleman was referred to our Department with complex medical history.

At the age of 47 (1996), he presented elsewhere to a Diabetic Clinic following pancreatitis with uncontrolled diabetes, hypertension, hyperlipidaemia and obesity. The appropriate medical treatment was initiated. Unfortunately, he was lost to follow up.
Eight years later (2003), he presented with headaches, visual disturbances and right 3rd and 6th nerve palsies. The MRI scan showed expanded fossa with tumour extending into the right cavernous sinus but no evidence of chiasmal compression. The hormonal evaluation revealed prolactin 999mIu/L (0-400), IGF-I 84 ng/ml (71-290), FT4 7.9 pmol/L (9.14-23.4) with low TSH. Short Synthathan test was normal but ACTH at time zero of 113ng/L (0-46). One collection for 24 hour urinary free cortisol was normal. The diagnosis of non-functioning pituitary adenoma was made. Thyroid hormone replacement was started. Preoperatively, atrial fibrillation and inferior myocardial infarction developed and finally TSA was done in 2004. Following surgery, the eye movements went to normal. The histology showed a heavily stained ACTH pituitary adenoma. Post TSA assessment showed 9am cortisol of 176nmol/L and thyrotroph and gonadotroph deficiencies.

Current presentation and further investigations: 4 years later (2008), he was referred to our Department with a progressive right 3rd nerve palsy and visual field defects. Two collections for 24 hour urinary free cortisol were high [650 and 891 (normal 0-560 nmol/L)]. Midnight cortisols were 792nmol/L and 804nmol/L. He failed to suppress on both low dose and high dose dexamethasone suppression tests. There was no response to CRH test. MRI pituitary showed a large multi-lobulated sellar (1.7X2.0x1.9cm) and supra sellar mass lesion (1.9X2.1X2.2cm) and right cavernous sinus was encased by tumour.

Treatment: Initially Metyrapone was started. Unfortunately he did not tolerate this medication. After considering all the operative risks and benefits, second TSA was done on November 2008. The post operative 9 am cortisol results were 767 and 1049 nmol/L. His right 3rd nerve palsy remained. Histology confirmed corticotroph pituitary adenoma. Post operative MRI showed a reduction in size of the sellar component but residual tumour persisted and the suprasellar component had not altered. Medical treatment was re started with Metyrapone and Fluconazole but stopped again due to side effects. He has been referred for radiotherapy.

Discussion: This case illustrates the difficulties encountered in the diagnosis and the management of silent corticotroph adenoma which can progress to aggressive clinical Cushing's disease. The discussion points are:
The management and follow up of silent Corticotroph pituitary adenoma including the role of radiotherapy.
The management of aggressive Cushing's disease after two transsphenoidal surgeries with intolerance to current medical therapies.
Role of bilateral adrenalectomy in the management of refractory Cushing's disease.
Diagnosis of Cushing's disease when the responses to high dose dexamethasone suppression test and to CRH test are not typical.
The Importance of the continuity of patient care.

11. A case of recurrent Cushing's Disease
HS Chahal, I Sabin, J Evanson, N Plowman, M Korbonits, AB Grossman. St Bartholomew's Hospital, (London)

We report a case of a female patient who presented to her local endocrinologist at the age of 20 years with a 4-year history of secondary amenorrhoea, hirsutism and weight gain of 7 stones. She had clinical signs consistent with Cushing's syndrome. Biochemistry showed lack of diurnal cortisol variation and failure of cortisol suppression on both the low-dose (2+0: cortisol 839nmol/L, 2+48 cortisol 741nmol/L) and high-dose dexamethasone suppression tests (8+48 cortisol 731nmol/L). An MRI demonstrated a poorly-enhancing area of pituitary tissue on the left side of the gland, extending into the cavernous sinus.
She underwent 3 transsphenoidal operations without any clinical or biochemical cure. Histology from the second operation confirmed Crooke's hyaline change, but no definite adenoma was found. She was referred to St Bartholomew's Hospital at the age of 21 years for a second opinion. An MRI revealed a left-sided pituitary lesion with extension into the cavernous sinus and no optic chiasm involvement. A bilateral petrosal sinus catheter confirmed a left-sided pituitary site of origin for the ACTH. As the patient's Cushing's disease had proved resistant to surgical therapy, it was felt that external beam

radiotherapy was the most appropriate option and she was administered 45Gy via 3 portals in 25 fractions over 32 days. However, despite being on metyrapone 750mg tds and ketoconazole 400mg bd, she still had Cushingoid features and an excess cortisol burden with a mean day-curve cortisol of 382nmol/L, and she underwent a bilateral adrenalectomy at the age of 22 years. Following this procedure, she lost 6 stones in weight with resumption of her menstrual cycle, and her clinical signs improved dramatically. Three years post adrenalectomy her plasma ACTH was elevated at 1053 ng/L (a 15-fold increase from her initial diagnosis at the age of 20 years) with a repeat MRI still showing residual disease in the left cavernous sinus, so she underwent targeted radiosurgery. Currently, one year after the radiosurgery, her ACTH level has reduced to 630 ng/L, with an MRI showing no increase in size of her residual tumour and she is on oestrogen, hydrocortisone and fludrocortisone replacement. She has an AGHDA score of 5/25 with a low IGF-1 level of 109ng/ml (117-358), but on an ITT her peak GH rose to 11mu/l.
In summary we present a young female patient with recurrent Cushing's disease who has had 3 transsphenoidal operations, external beam radiotherapy, bilateral adrenalectomy and targeted radiosurgery. We would like to ask the panel: 1) should a bilateral adrenalectomy have been performed or would the panel have continued with medical therapy, awaiting the effects of external beam radiotherapy; 2) given the recurrent nature of her disease, should the patient be treated with growth hormone if she is biochemically growth hormone deficient in the future; and 3) what would be their management plan in the future if the ACTH levels start rising and there is still residual disease on MRI?

12. Persistent pituitary Cushing's syndrome
V Bravis, D Morganstein, W Dhillo, F Roncaroli, E Hatfield, K Meeran Imperial, (London)

A 36-year old lady presented to another institution with hypertension, weight gain, change in body habitus and glucose intolerance. Her 24-hour urinary cortisol was raised at 2,000 nmol/24h and MRI of her pituitary revealed a 9mm adenoma. She failed to suppress her cortisol during a low dose dexamethasone suppression test. The adenoma was removed with transphenoidal surgery but her morning cortisol the day after the operation was raised at 400 nmol/L. She then had a second operation, which led to morning cortisol suppression down to 60. Two months later, whilst on replacement therapy, her symptoms and hypertension recurred. A repeat MRI revealed evidence of residual tumour. She underwent a third operation, which led to a short-lived fall in cortisol and she represented with persisting pituitary Cushing's with hypercortisolaemia and symptoms of fatigue, tremor, bloating and shortness of breath on exertion.
She was referred for a second opinion. A cortisol day curve revealed elevated cortisol levels throughout the day (786, 635, 499, 499 nmol/l) and she failed to suppress on a low dose dexamethasone suppression test, with an inappropriate rise after CRH administration. MRI did not show any residual pituitary adenoma. Review of the histology from her initial surgery confirmed a corticotroph adenoma. Ketoconazole treatment was commenced but resulted in a drug induced hepatitis. She was therefore restarted on high dose Metyrapone.
Questions for the panel:
What is the appropriate next step? A bilateral adrenalectomy or 4th pituitary operation? If she has an adrenalectomy what is the risk of Nelson's and should she have pituitary radiotherapy?

Forum 4

Chairs: Drs S Baldeweg (London) & J Ahlquist (Southend)

13. A case of acromegaly without radiological evidence of a pituitary tumour
SR Mehta, BMC McGowan, O Chaudhri, A Mehta, ECI Hatfield, T Tan, K Meeran, (Imperial, London)

A 62 year old gentleman was referred with a history of frontal headaches, excessive sweating, lethargy, joint pains, reduced libido and erectile dysfunction. In addition, he had noticed an increase in his shoe size and that his rings no longer fitted him. His past medical history comprised of primary hypothyroidism treated with thyroxine, multiple angiomatous glomus tumours, and a previous transient ischaemic attack. On examination he had a deep voice, some coarsening of his facial features, and enlargement of his hands and tongue. He had a prominent kyphosis of his spine and multiple pigmented skin lesions (consistent with angiomatous glomus tumours). Tinel's sign was positive, suggesting the presence of carpal tunnel syndrome. Baseline blood tests showed an elevated IGF-1 of 56.3 nmol/L (6-30) and evidence of secondary hypogonadism [LH <0.5 IU/L (2-12), FSH 1.4 IU/L (1.7-8.0), Testosterone 2.5 nmol/L (10-30)]. TSH was 1.18 mU/L(0.3-4.2), Free T4 16.5 pmol/L(9-26) and prolactin 198 mU/L(75-375). His growth hormone failed to suppress during an oral glucose tolerance test (basal 3.90 mg/L, nadir 3.71 mg/L) though glucose tolerance was normal (fasting glucose 4.7 mmol/L; 2h glucose 6.7 mmol/L). Based on the above clinical and biochemical features, a diagnosis of acromegaly was made. MRI pituitary, though technically challenging in view of his kyphosis, failed to demonstrate a convincing intra-pituitary lesion, but showed some evidence of skull vault thickening. Glucagon stress test showed an inadequate rise in cortisol from a baseline of 201nmol/L to a peak of 375 nmol/L, so hydrocortisone replacement therapy was commenced. We have not been successful in locating a laboratory to do a GHRH assay.
Points for discussion include:
(1) Does this gentleman have pituitary acromegaly?
(2) What is the likelihood that he has a GHRH secreting tumour, and what tests should be performed?

14. Acromegaly and colorectal carcinoma.
Miras A, Russell-Jones D, Hordern V

We would like to present the case of a 81 year old gentleman presenting with acromegaly and colorectal carcinoma.
Mr NH of good health and on no medication, presented in November 2005 to the colorectal team with anaemia and rectal bleeding. A colonoscopy and biopsy revealed an adenocarcinoma of the ascending colon. He underwent a laparoscopic right hemicolectomy. Histology unfortunately showed evidence of blood vessel and lymph node invasion. CT imaging of his chest, abdomen and pelvis did not show evidence of distant metastases. Following surgery he underwent adjuvant chemotherapy with 5FU and Leucovorin.
Serial CT imaging in 2006-7 showed no evidence of recurrence or metastases and his CEA remain undetectable. In April 2007 it was noticed by the surgical team that he had acromegalic characteristics. An IGF-1 level came back as 72 and an OGTT did not suppress GH levels (23.4mu/l). MRI of his pituitary (available) showed a pituitary microadenoma 8mm in diameter. The rest of his hormonal axes were intact but he did have impaired glucose tolerance. Pictures of the patient over the years (available) show a definite change of his habitus and facial characteristics from the 1970s onwards.

While he was undergoing endocrinological workup a staging CT showed two metastatic deposits in the liver and one in his lung. Following this further chemotherapy was commenced in the form of Oxaliplatin/de Gramont and he also underwent radiofrequency ablation of the metastatic deposits.
The patient lost a lot of weight, is frail and pituitary surgery is not without risk.
Octreotide was started to control his GH levels but he suffered from severe gastrointestinal side effects even at low doses therefore it was discontinued.
Cabergoline has been started and we are waiting to see his response.
The questions that this case raises are:
Would treatment of this patient's active acromegaly improve his oncological prognosis?
Is cabergoline likely to control his disease?
Should Pegvisomant be considered even though its gastrointestinal side effects may be intolerable?
Should radiotherapy be considered? Would its effects on GH reduction occur soon enough for clinical benefit?

15. Radiation induced meningiomas, a potential complication post treatment for acromegaly
Lecamwasam V, Abbara A, Lecamwasam K, Rafique A, Bell R, Baynes K (Ealing, London)

A 40-year-old lady was diagnosed with acromegaly in 1993 after presentation with clinical symptoms. Pituitary imaging showed a 1 cm pituitary lesion and she underwent transphenoidal hypophysectomy in 1993. Post-operatively she was rendered hypopituitary, but still had biochemical evidence of active acromegaly. Aside from steroid and thyroxine replacement, bromocriptine was commenced. She also underwent external beam radiotherapy.
On routine review in 2006, there were no features of acromegaly. But a surveillance pituitary MRI revealed an asymptomatic incidental 1.5 cm right parafalcine tumour.

This was treated conservatively.
In 2007, she complained of right facial neuropathic pain and a fifth cranial palsy was present on clinical examination. A repeat MRI brain imaging showed a new lesion arising lateral to the right cavernous sinus from the dural tail of the petrous bone.
She underwent an orbito-zygomatic craniotomy and excision of this lesion. Histology confirmed an atypical meningothelial meningioma with brisk mitotic activity with 80% of cells expressing progesterone receptor.
We believe that the meningiomas reported in this case were induced by radiation and fulfil the diagnostic criteria.
There are no conclusive prospective studies to fully assess the excess risk of non-pituitary cerebral malignancies secondary to radiotherapy.
This potential late occurrence should be considered for patients who have had radiotherapy for pituitary disease.

16. A future pregnancy in acromegaly?
Pererra S, BaldewegS (UCLH, London)

We present the case of a young patient with severe acromegaly due to a macroadenoma diagnosed in her first pregnancy. She has undergone several surgical procedures and radiotherapy and would like to have another child.