Twelfth Clinicopathological Conference on Pituitary Disease

Programme And Abstract Book

Wednesday 10th February 2010,
Royal College of Physicians, London

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Programme

9:25 **Welcome and Introduction** – Mr M Powell, London

Case 1: Refractory Hyponatraemia and an Extensive Sella tumour
C Feeney, A DeSilva, O Chaudhri, A Mehta, N Mendoza, F Roncaroli, ECI Hatfield, K Meeran' - London

Case 2: A Case of Sheehan's syndrome resulting in severe hyponatraemia
K Wynne O Chaudhri, T Tan and K Meeran. - London

Keynote lecture:
Hyponatraemia – a challenge for the endocrinologist
Dr S Ball, Newcastle

Forum 1: Variety of Pituitary cases
Chairs: Dr SE Baldeweg and Mr M Powell

Case 3: Hypothalamic-pituitary sarcoidosis – Role of Steroid therapy
K Muralidhara, D Kariyawasam, J Karalliedde, R Guzder, B McGowan, J Powrie, P Carroll – London

Case 4: Wegener's Granulomatosis presenting with visual loss and pituitary failure
G Mlawa, S Deshmukh A Nasruddin, DD Sandeman

Case 5: A Case of Langerhans Cell Histiocytosis X with pituitary and lung involvement
A Furness, M Piper, J Kung, R Herring, C Sinclaire, J Wright, S Davidson and D Russell-Jones – Guildford

Case 6: Optic Chiasm prolapse: Correlation of clinical and Radiological findings
G Plant A Shortt; I Davagnanam

11:20 Coffee and Posters

11:40 **Pituitary Foundation**
Kit Ashley, Director

11:50 **Forum 2: Aggressive pituitary cases**
Chairs: Dr MV Vanderpump and Miss J Grieve

Case 7: Acromegaly with multiple aggressive recurrences: Effect of temozolamide treatment
C Steele, I.A. MacFarlane, Mr M. Javadpour and Dr CDaousi – Liverpool

Case 8: A Case of aggressive macroprolactinoma resistant to dopamine agonist therapy and masquerading as an astrocytoma
TM Barber JAH Wass

Case 9: Temozolomide-induced regression of hepatic metastases in a Pituitary corticotroph carcinoma with low O^6-methylguanine-DNA-methyltransferase (MGMT) expression
AK Annamalai, H.Burton, N.Kandasamy, D.J.Halsall, K.Kovacs, A.Dean, N.Antoun, H.K.Cheow, S.Jefferies, V.K.K.Chatterjee, H.L.Simpson, R.W.Kirollos, J.D.Pickard, N.Burnet and M. Gurnell
Cambridge & Ontario

Case 10: Targeted Radionuclide therapy for metastatic pituitary Carcinoma
NL Fersht M.N. Gaze, J. Bomanji , S.E. Baldeweg and M.Powell – London

Case 11: Pituitary Metastasis – Approaches to diagnosis and Management
MA Saeed N Karavitaki and JAH Wass, Oxford

13:00 Lunch and Posters

13:50 Pituitary Apoplexy – National Guidelines
Chairs: Dr SE Baldeweg and Professor JAH Wass

Case 12: Recurrent acute pituitary apoplexy in a middle aged Man
A Martin, A Panahloo, L Seal - London

Case 13: Acromegaly after Apoplexy, Surgery, Radiotherapy and Growth Hormone Deficiency
C Steele, I.A. MacFarlane1, M. Javadpour and Dr C. Daousi - Liverpool

Pituitary Apoplexy Presentation
Dr S Kumar, Oxford

14:30 Forum 3: Cushing's Disease cases
Chairs: Dr GS Conway and Miss J Grieve

Case 14: The Changing Nature of Cushing's disease?
CE Gilkes, S Lightman, A Levy, T Ulahannan, J Reckless, Nelson R J

Case 15: A Complex case of Nelson's Syndrome
O Koulouri, M J Levy, I Robertson, J Elson, T A Howlett, Leicester & Nottingham

Case 16: A Difficult case of Cushing's syndrome
U Srirangalingam, D. Berney, F. Kaplan, W.M. Drake, London

Case 17: Evaluation of Transphenoidal Surgery for Cushing's Disease
V A Elwell, P Goetz, S E Baldeweg, SE and MP Powell – London

15:30 Afternoon tea and Posters

15:50 **Endocrine Outcomes of endoscopic Surgery**
Chairs: Mr N Dorward and Mr M Powell

Case 18: The surgical challenges of a Giant Craniopharyngioma: An operative case demonstrating The utility of image-guidance
R Chelvarajah, J Ahlquist and J Benjamin - Essex

Case 19: Transnasal endoscopic repair using a nasaseptal flap of CSF leak secondary to invasive pituitary tumour
AR Jesurasa, B Thakur, TA Carroll, S Mirza, S Sinha

Keynote Lecture
Mr N Dorward, London

16:55 **Poster and presentation prizes - Dr GS Conway**

17:00 Close

Abstracts

Case 1: Refractory Hyponatraemia and an Extensive Sellar Tumour

Author(s):
C Feeney[1], A DeSilva[1], O Chaudhri[1], A Mehta[2], N Mendoza[3], F Roncaroli[4], ECI Hatfield[1], K Meeran[1]
[1]Endocrine Unit, [2] Department of Radiology, [3]Department of Neurosurgery, [4] Neuropathology Unit, Imperial College Healthcare NHS Trust, London. W6 8RF.

A 29 year-old Ethiopian man presented with marked visual loss bilaterally, headache, systemic upset and significant hyponatraemia (115 mmol/L). MRI brain imaging demonstrated a large, lobulated, sellar and suprasellar mass, elevating the floor of the 3rd ventricle and compressing the optic chiasm. Pituitary profile on admission was as follows: FSH <0.5 IU/L, LH 0.1 IU/L, testosterone 0.9 nmol/L, TSH 0.66 mU/L, T4 6.8 pmol/L, ACTH 13 ng/L, IGF1 6.7 nmol/L, prolactin 90mU/L. An evening cortisol was 406 nmol/L. Plasma osmolality was 242 pOsmol/kg paired with a urine osmolality of 601pOsmol/kg. Hydrocortisone (im 50mg qds) and thyroxine (50 µg od) was commenced prior to transfer to our neurosurgical centre.

On admission, repeat biochemistry was: Na 122 mmol/L, serum osmolality 245 pOsmol/kg, urine osmolality 527 pOsmol/kg, urine sodium 158 mmol/L. The patient was assessed as being euvolaemic and so assigned a provisional diagnosis of SIADH. Fluid restriction to 500mls oral intake/24hrs for 5 days failed to make any improvement on plasma sodium levels and initially worsened them. Despite this, the patient continued to pass relatively large volumes of urine (up to 4L/24hrs) with urine sodium concentrations consistently over 100 mmol/L. A hypovolaemic state ensued which widened the differential diagnosis to include cerebral salt wasting syndrome (CSWS). Salt depletion was initially treated using isotonic saline (0.9%), but subsequently required hypertonic saline (1.8%), oral sodium and fludrocortisone to augment sodium levels to a maximum level of 128 mmol/L prior to surgery.

The patient underwent a transphenoidal resection of the mass followed by a debulking procedure via craniotomy one week later. Histology demonstrated a sellar neuroblastoma: a tumour which is rarely found in this anatomical site. Subsequent immunohistochemistry has shown 30% staining for anti-diuretic hormone antibodies, making this tumour extremely unusual. Post-operatively sodium levels have near normalised, but urine sodium concentrations are still high.

Our question for the expert panel is:

1. Is the diagnosis of CSWS based on his hypovolaemia, continuing negative fluid balance and excessive salt loss or one of cranial SIADH in view of the histology findings?
2. If we think this is cranial SIADH, how can we explain the large urine volumes produced?

Case 2: A Case of Sheehan's Syndrome Resulting in Severe Hyponatraemia

Author(s): K Wynne, O Chaudhri, T Tan and K Meeran. Endocrine Unit, Imperial College Healthcare NHS Trust, London. W12 0NN.

A 32 year old lady was admitted with a two day history of extreme fatigue, severe headache, vomiting, postural dizziness and blurring of peripheral vision on left lateral gaze. Two days previously she had undergone emergency caesarean section at 29 weeks gestation for an anterior uterine rupture. During the operation she lost 1.5 litres of blood and became hypotensive with a blood pressure of 87/54 mmHg. She was unable to lactate post-partum. On examination, she was confused, slow to respond and intravascularly deplete. Her blood pressure was 98/60 mmHg, pulse rate 80 beats per minute and respiratory rate 14 breaths per minute. Neurological examination demonstrated a left VIth cranial nerve palsy. Her visual fields were full to confrontation and dilated fundoscopy was unremarkable.

Investigations: sodium 116 mmol/L (138 mmol/L immediately post-operatively); potassium 3.7 mmol/L; serum osmolality 240 mOsm/kg; urine osmolality 535 mOsm/kg; urine sodium concentration 91 mmol/L. Baseline pituitary function testing revealed low 9 am cortisol, and hypogonadotrophic hypogonadism with a relative hypoprolactinaemia for the immediate postpartum period (9 am cortisol <30 nmol/l, ACTH <5ng/l, TSH 0.88 mU/l, free T4 9.1 pmol/l, LH <0.5, FSH 1.0, oestradiol <70 pmol/L, prolactin 375 mU/l). Magnetic Resonance Imaging of the pituitary gland demonstrated a central pituitary infarction. She was diagnosed with Sheehan's syndrome.

Severe hyponatraemia due to hypopituitarism can be life-threatening, but it is an often overlooked cause of low serum sodium. Hypocortisolaemia must be considered early as prompt treatment with steroids is effective and potentially life-saving. The hyponatraemia is caused by an inability to excrete a water load appropriately in the absence of glucocorticoid. In hypopituitarism, secondary hypothyroidism may also contribute to hyponatraemia. Following hydrocortisone replacement this patient's serum sodium improved to 122 mmol/L and her urine sodium fell to 38 mmol/L with complete resolution of her neurological deficit within 48 hours.

Case 3: Hypothalamic-pituitary sarcoidosis –Role of steroid therapy

Author(s): K Muralidhara, D Kariyawasam, J Karalliedde, R Guzder, B McGowan, J Powrie, P Carroll
Guy's and St Thomas' NHS Foundation Trust, London

From: Koteshwara Muralidhar [mailto:muraliks@doctors.org.uk
Author(s): K Muralidhara, D Kariyawasam, J Karalliedde, R Guzder, B McGowan, J Powrie, P Carroll
Guy's and St Thomas' NHS Foundation Trust, London

From: Koteshwara Muralidhar [mailto:muraliks@doctors.org.uk

Neurosarcoidosis, which occurs in approximately 5% of patients with systemic sarcoidosis, rarely presents as an isolated hypothalamic-pituitary lesion. The clinical management of such cases is difficult and needs long term monitoring due to a variable natural history. We report a case of a large hypothalamic-pituitary mass due to neurosarcoidosis, which showed good response to steroid therapy.

A 38-year-old South Asian man was referred to Guy's and St Thomas' Hospitals with a four-month history of tiredness, increased thirst, polyuria, loss of libido and erectile dysfunction. He had no visual symptoms or headaches. He had no history of exposure to tuberculosis. Clinical examination was normal with the exception of cervical lymphadenopathy. Visual field was full to confrontation, and this was confirmed on Goldman perimetry. Investigations revealed a picture of panhypopituitarism with a low FT4 (7.6pmol/l, NR:12-22 pmol/l), a low normal TSH (0.58mIU/l, NR:0.27-4.2mIU/l), undetectable gonadotropins and low testosterone (<10nmol/l). He had a high serum osmolality (305mOsmol) and a water deprivation test confirmed diabetes insipidus. A serum ACE level was elevated (166.4U/l, NR:8-52U/l). Histology from a cervical lymph node biopsy revealed non-caseating granulomata suggestive of sarcoidosis. An MRI demonstrated a gadolinium enhancing pituitary mass (17mmx17mmx13mm) involving the stalk and abutting the optic chiasm. A chest CT scan showed hilar lymphadenopathy but no parenchymal involvement. He was started on replacement doses of hydrocortisone, thyroxine, testosterone and desmopressin. An interval pituitary MRI at six months did not show any change in the size of the tumour. He was given a trial of prednisolone (40mg/day) as the tumour was close to the optic chiasm. An MRI following six-weeks of prednisolone showed a dramatic reduction in the size of the pituitary mass (7mmx4mmx6mm). The dose of prednisolone was tapered over six weeks to 10mg/day. He will be clinically monitored along with interval pituitary MRI and biochemical tests.

Case 4: Wegener's granulomatosis presenting with visual loss and pituitary failure.

Author(s): Mlawa G, Deshmukh S, Nasruddin A, Sandeman DD

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Introduction: Wegener's granulomatosis is an anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis of small and medium-sized vessels.Pituitary involvement in Wegener`s granulomatosis is rare and few cases have been reported previously.Isolated pituitary involvement in Wegener's granulomatosis is rare and is usually associated with other organ involvement (96% of cases) - commonly upper respiratory tract (93%), lung(73%) and kidneys(67%).

Case: We present a case of a 46 year old man who was admitted for investigation of visual loss. He had a 2-3 months history of blurring of vision,headaches(retro-orbital discomfort), red left eye, arthragia and epistaxis. His visual acuity was 6/60, with a central scotoma. MRI pituitary revealed an inflammatory looking mass involving the hypothalamus and infundibulum suggestive of hypophysitis. While inpatient he was diagnosed with diabetes insipidus and hypopituitarism. (FSH 1.0iu/L, LH <0.2iu/L, Testosterone <0.4nmol/L, TSH 0.03mu/L, FT4 7.4pmol/L, Prolactin 83miU/L).

Due to recurrent epistaxis, an ENT opinion was sought and nasal biopsy histology was diagnostic of Wegener's granulomatosis, backed by positive ANCA and elevated ESR (79mm/hr). He was treated with high-dose steroids and cyclophosphamide with remarkable improvement of his symptoms. His visual acuity improved as well as his central scotoma and red eye and normalisation of ESR. Repeat MRI pituitary revealed substantial resolution of the mass. He was commenced on thyroxine and testosterone replacement.

Conclusion: Wegener's granulamatosis is a rare cause of pituitary failure and should be considered in the differential diagnosis of hypophysitis. Multisystemic symptoms, such as demonstrated in our case should alert to this possibility as isolated pituitary involvement is unlikely.

Case 5: A case of Langerhans Cell Histiocytosis X with pituitary and lung involvement.

Author(s): Andrew Furness, Mark Piper, Jane Kung, Roselle Herring, Colin Sinclaire, John Wright, Sue Davidson and David Russell-Jones.

From: Andrew James Scott Furness [mailto:andrewfurness@doctors.org.uk]

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A healthy 24-year-old female presented with polydipsia, polyuria and lethargy. There was no significant past medical history and she was on no regular medication. Initial investigations showed an elevated sodium of 148mmol/L and urine osmolality of 118mmol/kg. Subsequent water deprivation testing was diagnostic of cranial diabetes insipidus. MRI Pituitary suggested increased thickness of the infundibulum consistent with a small tumour or inflammatory mass. She responded well to DDAVP but later represented with secondary amenorrhoea following a miscarriage. FSH/LH and oestradiol levels were low consistent with hypogonadotropic-hypogonadism. An insulin stress test, combined TRH and LHRH were performed to evaluate anterior pituitary reserve, these demonstrated impaired growth hormone and borderline cortisol responses to stimulation. Repeat MRI demonstrated no interval change raising the possibilty of an evolving panhypophysitis. Differential diagnosis included histiocytosis, sarcoid and lymphocytic hypophysitis.

Pituitary replacement included thyroxine, hydrocortisone, growth hormone and desmopressin. She was lost to follow up for a short period of time during which replacement therapy was suboptimal. She represented with recurrent infections. MRI Brain demonstrated no change and replacement therapy was recommenced. She later developed increasing lethargy and breathlessness which prompted further investigation, inflammatory markers were raised and chest radiograph demonstrated new bilateral nodular shadowing. HRCT confirmed diffuse pulmonary shadowing and histology following VATS biopsy was consistent with Histiocytosis X. The patient is increasingly symptomatic from her lung disease and is to undergo 6 cycles of 2-chlorodeoxyadenosine chemotherapy, a purine analogue which inhibits adenosine deaminase used in the treatment of hairy cell leukaemia.

The interesting question is whether this therapy will lead to improvement in pituitary function as well as her chest disease.

Case 6: Optic chiasm prolapse: Correlation of clinical and radiological findings.

Author(s):Gordon Plant; Alex Shortt; Indran Davagnanam

From: Gordon Plant [mailto:gordon@plant.globalnet.co.uk]

Objective. To determine whether there is a correlation between clinical and radiological findings in patients with optic chiasm prolapse.
Design. Retrospective case series.
Inclusion criteria. Patients with optic chiasm prolapse secondary to an empty sella as a result of medical treatment, surgical treatment or complications of pituitary disease.
Methods: For each patient the visual acuity, colour vision and visual field were correlated with the radiological findings. Chiasmal prolapse was classified as tractional or non-tractional and deviation from the midline was documented .
Results: Seven patients with optic chiasm prolapse were managed over a ten year period from 1999 to 2009, six following treatment for macroadenoma and one a Rathke's pouch cyst. Following surgery six of the seven patients experienced an initial improvement in visual function but all patients had a subsequent deterioration due to chiamsmal prolapse occurring between two months and five years post surgery, three occurring within 12 months and the remaining four patients 3 or more years post surgery. Six of the seven patients were managed conservatively and have remained relatively stable or had a very gradual deterioration in the clinical findings. One patient required chiasmopexy with fat packing of the sella. The degree of prolapse was not associated with the severity of compromise of visual function. Tethering of the chiasm and deviation of the chiasm from the midline was noted in five out of seven cases. There was no consistent association between the direction of traction and the pattern of visual field loss.
Conclusions:
Chiasmal prolapse following transsphenoidal hypophysectomy is rare but may result in significant visual loss. In the majority of cases the visual loss is gradually progressive but may be managed conservatively.

Case 7: Acromegaly with multiple aggressive recurrences: effect of temozolamide treatment

Author(s): Dr C. Steele[1], Prof I.A. MacFarlane[1], Dr D Husband[2], Mr M. Javadpour[3] and Dr C. Daousi[1]
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A 34 year old lady presented in 1997 with acute pituitary apoplexy and underwent emergency transsphenoidal surgery (TSS) because of deteriorating vision. IGF-1 was 102 nmol/L and random GH 21.4 micrograms/L consistent with acromegaly. Histology showed somatotroph pituitary adenoma with apoplexy. Her acromegaly remained active therefore radiotherapy was administered and treatment with bromocriptine and long-acting somatostatin analogue (SSA) were commenced. After 9 years of static residual adenoma on serial pituitary MRIs, she experienced several massive, symptomatic recurrences and underwent repeat TSS followed by three debulking craniotomies for massive tumour recurrence and severe brainstem compression. Histology remained consistent with somatotroph adenoma. CT thorax-abdomen and pelvis showed no metastases. MRI performed following shunt revision after her last operation revealed large residual adenoma, with sphenoid sinus and posterior nasal-cavity invasion. Seizure control became problematic with worsening of memory and cognitive function. IGF-1 and random GH continued to increase despite maximal medical therapy. In May 2009 she was prescribed off-license the first cycle of oral temozolamide at a dose of 150 mg/kg/m^2 given for 5 days in 28-day cycles. Follow-up MRIs to assess treatment response after 3 and 6 cycles of temozolamide showed stable appearances of her residual adenoma for the first time in the last 2 years. She has had no further compressive symptoms or episodes of raised intracranial pressure, no recent hospital admissions, she has remained seizure free for the last 6 months, cognitive function is stable and quality of life has improved; biochemical control though of her acromegaly has not yet been achieved.

Temozolomide has had some encouraging results in a small number of pituitary carcinomas and aggressive adenomas resistant to conventional treatment. One previous published case report has described a GH-secreting adenoma unresponsive to temozolamide. This represents the first case of an aggressive GH-secreting adenoma responding favourably to temozolamide treatment.

Case 8: A case of aggressive macroprolactinoma resistant to dopamine agonist therapy and masquerading as an astrocytoma

Author(s): Barber, TM; Wass, JAH

barberdoc9@aol.com [mailto:barberdoc9@aol.com]

The case is that of a 41 year-old doctor who presented originally in India with a right temporal visual field defect in 1994. CT scan showed an extensive supra-sellar lesion which was excised via craniotomy. Histology was reported as grade II astrocytoma. He made a good post-operative recovery, and moved to the UK in 1995. Repeat MRI scan in 1998 showed considerable enlargement of the tumour, and his serum prolactin was noted to be 47,000mIU/l. He was referred to the Endocrine Unit in Oxford.

Clinical assessment revealed galactorrhoea. Histological re-assessment of material obtained in India showed positive staining for prolactin, confirming a diagnosis of macroprolactinoma. Biochemistry showed LH 1.47mIU/l, FSH 2.4mIU/l, testosterone 4.5nmol/l and TFT normal. During the first week of bromocriptine therapy, prolactin suppressed to 30,000mIU/l. Due to intolerance of bromocriptine after one month, he was switched to cabergoline (0.5mg twice weekly). Testosterone and hydrocortisone replacements were also commenced. After 6 months of cabergoline therapy, prolactin levels remained very high (20,454mIU/l). Despite a gradual increase of cabergoline dose to 2.5mg twice weekly over the next year, prolactin remained >16,000mIU/l. Repeat MRI at 2 years revealed enlargement of the macroprolactinoma. Following non-complete trans-sphenoidal resection in 2000, he underwent stereotactic radiotherapy. Post-operatively, desmopressin was commenced for DI, and cabergoline (3mg twice weekly) was continued. Although serum prolactin failed to respond to a trial of octreotide therapy (sst3-positive receptors), levels gradually improved over the subsequent 8 years (currently 550mIU/l). Post-radiotherapy, he was commenced on growth hormone replacement therapy, and had successful fertility treatment with human menopausal gonadotrophin.

This case illustrates the difficulties associated with the diagnosis and management of aggressive macroprolactinomas that are resistant to dopamine agonist therapy. It illustrates the potential for mis-diagnosis of macroprolactinoma on the basis of radiological appearance and histopathological features, and the need for re-assessment of histology in any patient where an initial histology report is inconsistent with clinical, biochemical and radiological features.

Case 9: Temozolomide-induced regression of hepatic metastases in a pituitary corticotroph carcinoma with low O^6-methylguanine-DNA methyltransferase (MGMT) expression

Author(s): A.K.Annamalai[1], H.Burton[1], N.Kandasamy[1], D.J.Halsall[2], K.Kovacs[3], A.Dean[4], N.Antoun[5], H.K.Cheow[5], S.Jefferies[6], V.K.K.Chatterjee[1], H.L.Simpson[1], R.W.Kirollos[7], J.D.Pickard[7], N.Burnet[6] and M. Gurnell[1]

Institute of Metabolic Science[1], Departments of Clinical Biochemistry[2], Pathology[4], Radiology[5], Oncology[6] and Neurosurgery[7], Addenbrooke's Hospital, Cambridge; Department of Pathology, St. Michael's Hospital, University of Toronto[4], Ontario, Canada.

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Background: Pituitary carcinoma occurs in ~0·2% of resected pituitary tumours, and carries a poor prognosis (mean survival <4 years), with standard chemotherapeutic regimens showing limited efficacy. However, recent evidence suggests that temozolomide, an orally active alkylating agent used principally in the management of glioblastoma, may also be effective in controlling aggressive/invasive pituitary adenomas/carcinomas. Low levels of expression of the DNA-repair enzyme MGMT, as assessed by immunohistochemistry, predicts temozolomide responsiveness. Here, we report a case of a pituitary corticotroph carcinoma with hepatic metastases, which responded clinically, biochemically and radiologically to temozolomide therapy.

Case report: A 65-year-old man presented as an emergency with frontal headache and evolving bilateral 3rd nerve palsies. Imaging showed a sellar-based mass with parasellar and suprasellar extension. At transphenoidal surgery a necrotic ACTH-staining pituitary adenoma was resected. There were no features of Cushing's syndrome clinically or biochemically, and hydrocortisone replacement was required post-operatively. No residual tumour was identified on post-operative MRI and the patient elected for surveillance follow-up.

However, two years later he developed clinical and biochemical evidence of ACTH-dependent Cushing's syndrome. Pituitary MRI showed no evidence of tumour regrowth and, although a peripheral CRH test suggested a corticotroph origin, IPSS did not demonstrate a central:peripheral gradient. Further imaging with CT and FDG-PET revealed multiple hepatic lesions, and subsequent biopsy confirmed metastatic ACTH-staining pituitary carcinoma. MGMT expression was very low in both the primary pituitary tumour and hepatic metastases.

Temozolomide therapy was commenced (200mg/m^2 daily for five consecutive days every 28 days) and has been well tolerated. ACTH levels have fallen from a peak of 5685 to 2318 ng/L after 5 cycles, with CT demonstrating partial regression of the hepatic lesions. Metyrapone and ketoconazole were also used to help control hypercortisolism and the patient has undergone pituitary radiotherapy to mitigate against the potential risk of local tumour recurrence.

Case 10: Targeted Radionuclide Therapy for metastatic pituitary carcinoma

N.L. Fersht[1], M.N. Gaze[1], J. Bomanji[2] , S.E. Baldeweg[3] and M.Powell[4]
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[3]Department of Endocrinology, UCLH
[4]Department of Neurosurgery, NHNN

We present an innovative treatment for a 64 year old patient with metastatic pituitary carcinoma.

He presented originally aged 41 years in 1987 with bi-temporal hemianopia and had a frontal craniotomy and resection of a pituitary adenoma, followed by adjuvant radiotherapy.
In 2006, he underwent transphenoidal resection of his recurrent pituitary adenoma. MRI at the time demonstrated meningeal thickening throughout the neuraxis and leptomeningeal nodules infra and supratentorially.
By June 2009 the primary tumour was stable but the meningeal thickening and leptomeningeal nodules had increased in size and number.
In August 2009 one of the spinal nodules was excised and confirmed the diagnosis of metastatic pituitary carcinoma (histologically resembling his original pituitary adenoma, both lesions being cytologically bland without elevation of the proliferation index or over expression of p53).

Pituitary carcinoma is an extremely rare condition (between 0.1 - 0.5% of all pituitary tumours) diagnosed by the presence of craniospinal and / or systemic metastases, rather than local invasion. It is thought to arise from a benign adenoma rather than *de novo*. No standard chemotherapy regime exists. Various combinations of drugs have been tried but with only temporary responses seen.

As significant numbers of neuroendocrine tumours express somatostatin receptors, we carried out a 68Ga-octreotate whole body PET-CT scan. This confirmed the presence of an Octreotate-avid pituitary adenoma recurrence with cerebral and bony skull Octreotate-avid metastases.
We decided to commence treatment with 177-Lutetium-Dotatate. This consists of a somatostatin peptide analogue, coupled with a complexing moiety (DOTA) labelled with the beta-emitter Lutetium-177. By targeting somatostatin receptor-positive tumours we may deliver a tumoricidal radiation dose. The treatment is well tolerated with minimal side-effects, and easy to administer requiring only a short in-patient stay in a radiation protected environment.

At UCLH we have now treated 17 patients with neuro-endocrine tumours with 177-Lutetium-Dotatate (including 4 children), each receiving up to four administrations three months apart. However, this is our first patient with a metastatic pituitary carcinoma.

Case 11: Pituitary Metastasis – Approaches to Diagnosis and Management

Author(s): MA Saeed, N Karavitaki and JAH Wass (Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford

From: cioman2@yahoo.com [mailto:cioman2@yahoo.com]f

History:
A 68-year-old male, presented 16-months after a stable, post-chemotherapy, right upper lobe pulmonary adenocarcinoma, with a 2-month history of headaches, right-sided visual disturbance, low libido and tiredness. He denied increased thirst and nocturia.
Examination:
There were no signs of hypersecretory endocrine conditions, and he had left-sided blindness from previous trauma, and right-sided superior temporal quadrantanopia, with intact cranial nerves.
Investigations:
1) normal renal and liver function; 2) normal adjusted calcium; 3) normal IGF-1; 4) secondary hypogonadism: LH <0.1 IU/L (1.5-9.3), FSH 0.3 IU/L (2-20) and 9am testosterone <0.4 nmol/L (8.4-28.7); 5) secondary hypothyroidism: TSH 2.12 mU/L (0.5-6.0) and FT4 8.8 pmol/L (11.5-22.7); 6) suboptimal short synacthen test (0min: 195 nmol/L and 30min: 506 nmol/L (>580)) and, 7) normal prolactin.
An MRI brain with gadolinium showed a 2cm x 2cm x 1cm intra and suprasellar, poorly enhancing mass, with significant compression of the optic chiasm – a possible metastasis involving the pituitary and hypothalamus.
Management:
Under hydrocortisone cover, because of the large suprasellar component, he had an elective craniotomy to decompress the optic chiasm. Histopathology confirmed a metastatic adenocarcinoma from the pulmonary primary lesion.
Postoperatively, he had ACTH deficiency and was replaced with hydrocortisone, and required Desmopressin for cranial diabetes insipidus.
He received adjuvant pituitary radiotherapy, and a bone scan confirmed he had metastasis to the bones for which he received lumbosacral radiotherapy.
The patient died 6-months from diagnosis of the pituitary metastasis.
Discussion: [1, 2]
Pituitary metastasis is mainly asymptomatic and can be missed due to symptoms common to advanced malignancy. The commonest presentation is diabetes insipidus. The primary sites are usually the breast and the lung (70%). Adequate replacement therapy, metastatic tumour resection, adjuvant radiotherapy and/or chemotherapy are advised for improved quality of life. The median survival time is 6 months.
References:

1. Komninos J, Et Al. 2004 Tumors Metastatic to the Pituitary Gland. J Clin Endocrinol Metab, 89(2):574-580
2. Morita A and Laws ER 1998 Symptomatic pituitary metastases. J Neurosurg 89:69-73

Case 12: Recurrent acute pituitary apoplexy in a middle aged man

Author(s): Dr Allison Martin, Dr Arshia Panahloo, Dr Leighton Seal
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A 41 year old man presented to Casualty with a 1 day history of sudden onset of severe headache, vomiting and a self limiting seizure in March 2004. He was severely hypotensive and hyponatremic. His initial CT head scan showed haemorrhage into a cystic pituitary mass later confirmed on MRI. Multiple anterior pituitary hormone deficiencies were diagnosed (growth hormone, gonadotropin, thyroid, cortisol) for which he had hormone replacement therapy. Serial formal visual field assessments were normal. He made a remarkable recovery and was kept under close surveillance by the neurosurgeons and endocrinologists.

A year later a repeat MRI showed an increase in the pituitary tumour size with involvement of the optic chiasm. Trans sphenoidal pituitary debulking surgery was performed and he was kept under close follow up by a multidisciplinary team of specialists. Fifteen months after his surgery, a routine MRI showed an increase in the size of the pituitary remnant. A month later he presented to Casualty with headache and seizures and a further apoplectic event was confirmed on MRI. He had radiotherapy in 2007 and has been stable ever since.

Pituitary apoplexy is a rare and potentially life threatening condition caused by a rapid enlargement of the pituitary gland due to haemorrhage or infarction into a pre-existing pituitary tumour. Patients may present acutely with headache, vomiting, visual disturbance and/or various pituitary hormone deficiencies or, sub clinically during pituitary imaging or surgery. Recurrent apoplexy is also exceedingly rare. The literature suggests early trans sphenoidal surgery is a safe and effective form of treatment for acute cases with visual disturbance. Radiotherapy is not recommended for the primary treatment of acute cases as the risk of tumour re growth is very small. Radiotherapy is usually reserved for patients with evidence of tumour re growth after pituitary surgery.

Case 13: Acromegaly after Apoplexy, Surgery, Radiotherapy and Growth Hormone Deficiency

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A 31-year old man with Holt-Oram syndrome presented in 2003 with severe headache, photophobia and bitemporal hemianopia, consistent with pituitary apoplexy. CT brain showed a large sellar mass with suprasellar extension and compression of the optic chiasm and 3rd ventricle. Emergency debulking transsphenoidal surgery (TSS) was performed because of symptomatic hydrocephalus. A pituitary adenoma with evidence of recent haemorrhage/infarction was removed. Histological examination was consistent with a GH-secreting adenoma. Postoperatively IGF-1 was 49(normal 15-40) nmol/L with nadir GH 1.5 micrograms/L during oral glucose load testing. He had no clinical features of acromegaly. Over the next 6 months IGF-1 remained raised 52 nmol/L with random GH 2 micrograms/L. MRI showed residual tumour and fractionated conventional radiotherapy was administered. Mild hypercalcaemia, with a positive family history led to diagnosis of gene-positive MEN type 1 syndrome.

In 2006 glucagon-stimulation testing revealed GH and cortisol deficiency (peak GH 1.8 micrograms/L, peak cortisol 466 mmol/L) with IGF-1 23 (normal 15-40) nmol/L. Despite hydrocortisone and testosterone replacement, he continued to complain of lethargy, his QoL-AGHDA score was only 7, therefore did not fulfill NICE criteria for a trial of GH replacement. In 2008 his IGF-1 and GH levels started to rise (IGF-1 49 nmol/L, random GH 2.1 micrograms/L) and developed coarse facial features and increased sweating. In 2009 GH suppressed to only 0.85 micrograms/L on oral glucose testing, IGF-1 was 58 nmol/L and repeat MRI showed static residual adenoma. He has been started on bromocriptine and treatment with a long-acting somatostatin analogue is being considered.

This is a very unusual case of recurrent acromegaly despite previous acute pituitary apoplexy, TSS and radiotherapy, treatments which had rendered this patient severely growth hormone deficient for a number of years. His current progress and the relevant literature will be discussed.

Case 14: The Changing Nature of Cushing's Disease?

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Background
The incidence of pituitary-driven Cushing's disease is approximately 1.2-1.7 per million [1]. In a regional pituitary service serving a stable population of approximately 2.5 M, a sudden increase in the proportion of MRI-negative Cushing's disease and in the rate of transphenoidal selective adenectomy for Cushing's disease prompted a change in surgical strategy and review of the casemix and caseload.

National Data
An analysis of the hospital FCE and admission rates for England and Wales between 1998 and 2008 for ICD10 codes specific for pituitary-driven Cushing's disease revealed a steady increase of 45% from 184 to 268 FCEs.

Regional Data
The annual rate of transphenoidal selective adenectomy for Cushing's disease, which had been stable at an average of 3-4/yr between 1991 and 2008, trebled to 9/yr in 2009.

Case-mix and outcomes
Of the 13 cases of pituitary-driven Cushing's disease treated by transphenoidal microsurgical exploration in 2008 and 2009, 11 (85%) had normal or equivocal pre-operative 1.5T MRI scans with and without contrast. Of these 'MRI negative' cases, a histologically-confirmed, corticotroph microadenoma was identified in 5 (45%). Although lower remission rates are recognised in patients without histological evidence of adenoma [2], at this early stage all of the patients are in clinical remission; 7 patients are in endocrine remission or have persisting hypocortisolaemia requiring replacement and 4 are awaiting full post-operative endocrine assessment. 1 patient required a second pituitary exploration.

Proposal
These findings raise the possibility that the pathophysiology, incidence, detection rates, or intervention rates for pituitary-driven Cushing's disease in the UK are changing. The authors propose a national audit.

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Case 15: A complex case of Nelson's syndrome

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Case: A 16 year old woman presented with typical clinical and biochemical features of ACTH-dependent Cushing's syndrome. MRI revealed no discrete lesion but petrosal sinus sampling gave clear evidence of pituitary Cushing's disease. Despite two transsphenoidal operations, cortisol levels remained persistently elevated. She therefore underwent bilateral adrenalectomy 14 months after diagnosis with initial satisfactory biochemical results and regression of her cushingoid features. However, post-adrenalectomy she became pigmented, ACTH level (2-hour post-hydrocortisone) was elevated at 640 ng/L, and MRI demonstrated a new left sided macroadenoma confirming Nelson's syndrome. Conventional fractionated 3-field radiotherapy (45 Gy) led to a gradual suppression of ACTH levels (ACTH 183 ng/L three years after radiotherapy). MRI confirmed adenoma shrinkage. She remained stable for a further three years, but subsequently developed increasing pigmentation and diplopia. ACTH rose to 4967 ng/L and MRI showed extension of her adenoma. After transsphenoidal resection of the adenoma ACTH fell to 133 ng/L but 15 months later rose to 423 ng/L and subsequently 1250 ng/L with an increase in size of the residual adenoma. She therefore underwent gamma knife stereotactic radiosurgery and 6 months post-gamma knife her pituitary adenoma is currently stable in size. Complexity is further increased by her current desire to conceive in the context of panhypopituitarism and endometriosis.

Discussion: This patient developed all the possible anticipated problems at each step of the management pathway for Cushing's disease. Current desire for pregnancy provides a focus for discussion of the complex medical, surgical and radiological issues involved in her future management. Is ovulation induction appropriate at this stage or should the patient be advised to wait? Should any additional treatment be considered at this stage? What are the options if pituitary enlargement should occur in a future pregnancy?

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Case 16: A difficult case of Cushing's syndrome

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A 49 year female presented to an outside unit with classical features of Cushing's syndrome confirmed biochemically with a failure to suppress on a standard 48 hour low dose dexamethasone suppression test, elevated urinary free and midnight cortisols. ACTH levels were undetectable and a 3cm lesion in the right adrenal prompted a diagnosis of Cushing's syndrome secondary to an adrenocortical adenoma. A right adrenalectomy was performed however the patient remained biochemically uncured postoperatively with ongoing symptoms. A CT scan confirmed an unintentional subtotal right adrenalectomy. The patient was referred to our unit for assessment.

Question 1 - Completion adrenalectomy or re-investigate?

Clinical and biochemical assessment confirmed cyclical Cushing's syndrome, with detectable ACTH levels suggesting ACTH dependent disease. Further histological review of the partial adrenalectomy suggested some features in keeping with a diagnosis of low grade adrenocortical carcinoma.
The patient underwent inferior petrosal sinus sampling which confirmed an unequivocal central to peripheral gradient and lateralisation to the left side of the pituitary. A pituitary MRI identified a left-sided lesion in keeping with a microadenoma. In view of the cyclicity of disease, the patient was pre-treated with a block and replace regime of metyrapone and hydrocortisone with clinical improvement judged by weight loss and reduced insulin requirement for type 2 diabetes. Attempted trans-sphenoidal selective microadenomectomy was not curative with fluctuating postoperative serum cortisol measurements. Crooke's change was evident on the resected specimen, but no adenomatous tissue was seen. She has been discharged on metyrapone and hydrocortisone, with ongoing weight loss and a falling insulin requirement and awaits further management.

Question 2 - What should the next step be in managing her Cushing's disease?

a. Medical therapy with metyrapone and hydrocortisone

b. Repeat trans-sphenoidal surgery

c. Pituitary radiotherapy and medical therapy in the intervening period

d. Bilateral adrenalectomy (possible diagnosis of adrenocortical carcinoma)

Case 17: Evaluation of Transsphenoidal Surgery for Cushing's Disease

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Objective: Transsphenoidal pituitary surgery is currently considered the treatment of choice for Cushing's disease. The early identification of patients with Cushing's disease, who undergo surgical intervention, allows for the opportunity of surgical cure and avoidance of the chronic complications of hypercortisolism.

Methods: A retrospective study of patients with pituitary-dependant Cushing's disease, who underwent elective transsphenoidal pituitary surgery, performed by single surgeon, was conducted. All patients underwent pre-operative investigation to confirm ACTH-dependant Cushing's disease, with localisation of ACTH-secreting source by imaging (MRI scans) and in a majority of cases by inferior petrosal sampling. Post-operatively, all patients underwent an endocrinological evaluation to establish their response to surgery. Analysis was performed by review of medical notes, an electronic database and consultations. In addition to demographic data, duration of symptoms, complications and outcomes were all collected.

Results: A consecutive series of 53 patients who underwent transsphenoidal pituitary surgery during a two-year period were evaluated. The mean age at surgery was 37.2. The mean interval at follow-up was 23.1 months (range 1-48 months). Overall, 44 patient (83%) were in remission at the time of follow-up. A total of 9 patients (17%) failed to achieve remission following surgery: 4 patients demonstrated a clinical improvement in their underlying symptoms but showed no biochemical improvement and a further 5 patients demonstrated no overall improvement following surgery. On post-operative radiological imaging, a total of 3 patients demonstrated residual disease invading the dura, cavernous sinus or adjacent structures.

Conclusions: Standard transsphenoidal surgery can provide complete remission in selected patients with Cushing's disease. It is important to identify positive predictive factors and stratify patients prior to surgery. An accurate diagnosis, tumour localisation and experienced surgeon are crucial for beneficial outcomes.

Case 18: The surgical challenge of a Giant Craniopharyngioma: an operative case demonstrating the utility of image-guidance

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Introduction
Craniopharyngioma is a sellar region tumour that poses a formidable surgical challenge mainly because of its large size at presentation with extension into diencephalic structures. Hence, consideration is often given to a trans-cranial approach which carries significant risk of hypothalamic deficit post-operatively. The trans-sphenoidal route is relatively safer but mesencephalic reach can be limiting. We describe an operative case in which image-guidance was employed to overcome this limitation in an elderly unfit patient.

Case History
A 74-year old Caribbean man with considerable anaesthetic risks presented with progressive visual deterioration and somnolence. Endocrine profile demonstrated panhypopituitarism. MRI scan showed appearances consistent with a large craniopharyngioma extending from the sellar region filling most of the third ventricle, extending into the left lateral ventricle anterior to the midbrain.

Operative Details
A decision was made to employ an extended microscopic trans-sphenoidal approach using MRI and CT fused image-guidance (STEALTH, Medtronics) in order to decompress the optic apparatus and minimize operative time.

Post-operative progress
After an initial stormy period that was complicated by diabetes insipidus and renal failure, the patient seemed to make good progress with considerable visual recovery. He is now maintained on long-term anterior and posterior pituitary replacement and anticonvulsants. The decompressed corridor is visible on post-op imaging. Visual improvement remains preserved.

Discussion
This case illustrates the operative technical challenges encountered in tumour excision from deep regions of the brain in which vicinity lie crucial areas such as the hypothalamus and upper brain stem. Image-guidance appears helpful in safely extending the reach of the trans-sphenoidal approach posteriorly. Fused CT and MRI image-guidance assists with both the bony landmark identification and in distinguishing tumour from surrounding neural structures respectively. Alternative surgical strategies include the trans-cranial route and an endoscopic approach, which may need consideration should re-treatment ever be required.

Case 19: Transnasal endoscopic repair using a nasoseptal flap of CSF leak secondary to invasive pituitary tumour

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Background
Endoscopic transsphenoidal surgery for resection of pituitary tumours has classically included reconstruction of the anterior wall of the sella turcica, using a variety of materials (both synthetic and natural) to recreate the original anatomy and prevent postoperative cerebrospinal fluid (CSF) leaks. Risk factors for CSF leak include revisional surgery, tumour size, consistency and resection margins. Complications of persistent leakage can include meningitis, tension pneumocephalus and post-infective hydrocephalus.

Objectives
To assess the role that nasoseptal flaps might play in preventing post-operative CSF leak after transsphenoidal surgery for pituitary tumours.

Methods
Two patients with CSF rhinorrhoea secondary to pituitary tumours underwent surgical repair of their anterior skull base defects with rotational nasoseptal flaps (pedicled on the sphenopalatine artery), with subsequent clinical follow-up for assessment of adequacy of repair.

Results
Both patients had successful repair of their anterior skull base defects using the nasoseptal flap, with no recurrence of the CSF rhinorrhoea post-operatively, or at clinic follow-up and no evidence of meningitis or hydrocepahlaus.

Conclusions
Rotational nasoseptal flaps provide a safe, effective and inexpensive method for reconstruction of the sella dura. The full use of this form of repair will need further evaluation with respect to other methods, but may obviate the need for tissue grafts, fibrin glue, or lumbar drain placement in patients with CSF rhinorrhoea secondary to pituitary tumours.