

Junior Members Forum, Thursday 22 November 2007

North lecture theatre, Medical Biology Centre, Belfast



PROGRAMME

A. PLATFORM PRESENTATIONS

1. Tumour Characteristics of False Negative Imprint Cytology In Patients Undergoing Sentinel Lymph Node Biopsy.

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Introduction: Sentinel Lymph Node Biopsy (SLNB) is set to become the standard of care for axillary staging in breast cancer. The aim of this study is to evaluate the tumour characteristics associated with false negative intraoperative imprint cytology.

Methods: Data was recorded prospectively for 105 consecutive patients with clinically node negative breast cancer. All had excision of the breast tumour and SLNB followed by axillary node clearance. Intra-operative imprint cytology was carried out in conjunction with post-operative haematoxylin & eosin (H&E) staining and immunohistochemistry (IHC).

Results: Forty-three patients (41%) had a positive sentinel node diagnosed. Nine cases were negative using imprint cytology. Of those 9 cases, 5 had micrometastases on H&E or IHC. Therefore there were 4 "true" false negative cases (9%). Of those cases that were "true" false negatives, the mean invasive cancer size was 27mm (8-60mm). Fifty percent of the tumours contained lobular elements. Median tumour grade was 2. All of the tumours were oestrogen receptor (ER) positive and 25% were HER-2 positive. Of the 34 remaining cases that were SLNB positive, the mean invasive cancer size was 32mm (12-70mm). Twenty-six percent of the tumours contained lobular elements. Median tumour grade was 2. Eighty-five percent of the tumours were ER positive and 9% were HER-2 positive.

Conclusion: The use of imprint cytology accurately identifies metastatic spread in the majority of patients undergoing SLNB. Although the numbers in this study are small, there are no obvious tumour characteristics associated with false negative imprint cytology in patients having SLNB.

2. Effect of ingestion of food on the inhibition of DPP-IV activity by oral metformin in Type 2 diabetes.

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Introduction: The incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) constitute the enteroinsular axis which promotes postprandial insulin secretion. The therapeutic potential of these hormones in diabetes is limited by their rapid inactivation by the enzyme dipeptidylpeptidase-IV (DPP-IV). Here we investigated the acute effects of metformin in the presence and absence of food on DPP-IV activity in Type 2 diabetes.

Methods: Ten subjects with Type 2 diabetes (6 male/4 female, age 65.8±15.8 years (mean ± SEM), body mass index 30.0±7.5kg/m², HbA1c 6.3±1.2%) received metformin 1g orally or placebo together with a standard mixed meal (SMM) in a random crossover design. Six subjects reattended fasting and received metformin 1g without a SMM.

Results: Following SMM (n=10), DPP IV activity was not suppressed by metformin compared with placebo (area under curve AUC_{0-4h} 1574±4 and 1581±8 µmol/min respectively). No differences were observed in plasma glucose, insulin and total GLP-1. After fasting (n=6), DPP IV activity was suppressed (P<0.02) when compared to those given metformin with a SMM (AUC_{0-4h} 1494±9 vs. 1578±4 µmol/min). Metformin plasma levels were significantly higher (P<0.03) after fasting than SMM (AUC^{0-4h} 457±55 vs. 350±66 mcg/ml).

Conclusion: Metformin inhibits DPP IV activity in patients with Type 2 diabetes in the fasting state but not when taken with a standard mixed meal. Metformin plasma concentrations are lower if taken with food. Metformin may have potential for combination therapy with incretin hormones.

3. Prosthetic stent-graft infection following endovascular abdominal aortic aneurysm repair

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Objective: The purpose of this report is to discuss the

incidence, diagnosis and management of stent-graft infections following EVAR¹.

Methods: Data were collected from the hospital database and medical case notes for all patients with infected endografts following elective or emergency EVAR for AAA over the last eight years in two university teaching hospitals in Northern Ireland. The data included the patient's age, gender, presentation of sepsis, treatment offered and the ultimate outcome. The diagnosis of graft related sepsis was established by a combination of investigations including inflammatory markers, labelled white cell scan, Computerized Tomography (CT) scan, microbiology cultures and post mortem examination.

Results: Out of a total of 509 patients, including 433 elective repairs and 76 emergency endografts for ruptured AAA, six suffered graft related septic complications. Two patients presented with left psoas abscess and were treated successfully with extra-anatomical bypass and removal of the infected stent-graft. A further two patients presented with infected graft without other evidence of intra-abdominal sepsis: one underwent successful removal of the infected prosthesis with extra-anatomical bypass while the other was treated conservatively and died of progressively worsening sepsis. The fifth patient presented with unexplained fever and died suddenly, with a post-mortem diagnosis of aorto-enteric fistula and ruptured aneurysm. The last patient presented with an aorto-enteric fistula, was treated conservatively in view of concurrent myelodysplasia, and died of possible aneurysm rupture.

Conclusion: This report is to emphasize the need for continued awareness of potential graft-related septic complications in patients undergoing endovascular repair of AAA. Attention to detail with regard to sterility and antibiotic prophylaxis, during stent-grafting and during any secondary interventions, is vital in reducing the risk of infection. In addition, early recognition and prompt treatment are essential for a successful outcome.

¹ Sharif MA, Lau LL, Lee B, Ellis PK, Blair PH, Soong CV. Prosthetic stent-graft infection following endovascular abdominal aortic aneurysm repair. *J Vasc Surg* 2007;**46**:442-448.

4. Patients with Primary (Idiopathic) Achalasia Have Circulating Peripheral Blood Mononuclear Immune Cells That Are Hyper- Reactive To the Herpes- Simplex -1 Virus

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Introduction: Achalasia is the best characterized oesophageal motor disorder but the aetiology is unknown. The pathology seen in achalasia consists of a decrease in nitric oxide-producing neurones and the presence of an activated T-cell inflammatory infiltrate in the myenteric plexus¹. Certain Human Leucocyte Antigen (HLA) class II alleles are also more

prevalent in patients with primary achalasia¹. These factors suggest that an autoimmune mechanism may be involved in the pathogenesis of primary achalasia. The stimulus initiating this is unknown but could involve the Herpes simplex -1 virus (HSV -1). A previous study has demonstrated the existence of oesophageal mononuclear immune cells reactive to HSV -1 antigens in an in- vitro setting².

Aims & Methods: The aim of this study is to test the hypothesis that circulating peripheral blood mononuclear cells in patients with primary achalasia may be reactive to HSV- 1. Whole blood culture experiments were conducted with heparinised peripheral venous blood obtained from 151 patients with primary achalasia and 118 healthy controls. Whole blood was cultured in the presence of ultraviolet inactivated HSV – 1 (multiplicity of infection of 1 TCID50 / lymphocyte) or conditioned cell culture media. Reactivity of mononuclear cells to viral antigens was quantified by measuring expression of the cytokine gene interferon – gamma using Taqman® Real Time Polymerase Chain Reaction. Data are expressed as cytokine fold change corresponding to ratio of interferon – γ messenger RNA copies produced in antigen stimulated versus unstimulated cells. Interferon- γ fold change was compared between cases and controls using the unpaired student's- t test after log transformation and expressed as median (interquartile range).

Results: The interferon- γ fold change was higher in cases 61.33 (20.54 – 217.00) than controls 49.67 (10.05 – 157.05). Mean fold change difference between cases and controls was 1.66 times (95% confidence interval 1.17 – 2.34, p = 0.02).

Conclusion: The results of this study indicate that mononuclear immune cells hyper- reactive to HSV- 1 are present in the peripheral blood of patients with primary achalasia and may contribute to the pathological changes observed in the myenteric plexus.

¹ Park W, Vaezi MF. Etiology and pathogenesis of achalasia: the current understanding. *Am J Gastroenterol* 2005;**100**:1404-14.

² Castagliuolo I, Brun P, Costantini M, Rizzetto C, Palu G, Costantino M, Baldan N, Zaninotto G. Esophageal achalasia: is the herpes simplex virus really innocent? *J Gastrointest Surg* 2004;**8**:24-30.

5. The value of PSA testing in men older than 65 years

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Introduction: Many men ≥ 65 years old have histological prostate cancer. Only a small proportion may present clinically with the disease and relatively few will die from prostate cancer. We assessed baseline PSA levels and the risk of clinically detected prostate cancer and prostate specific mortality in this population.

Methods: From a regional PSA database, all men aged ≥ 65 years old who had their first PSA test between 1994 and 1998 were identified. These were followed for prostate cancer diagnosis and mortality until 2003. The absolute risk and hazard ratio for prostate cancer diagnosis and mortality, based

on baseline PSA level, were determined.

Results: 36003 men were included. Mean age was 74.9 years and mean follow-up 5.4 years. 2153 (6.0%) men were diagnosed with prostate cancer. 13074 (36.3%) died, with prostate cancer the cause of death in 673 men (5.1% of deaths). Within age groups, the absolute risk and hazard ratio of cancer increased incrementally with PSA level (Table). Prostate-specific mortality remained low (<5/1000 person years) at all PSA categories <15.0ng/ml. All-cause mortality was similar in PSA categories <10.0ng/ml, and was much greater than prostate-specific mortality across all PSA categories.

Conclusion: The risk of prostate cancer diagnosis and prostate specific mortality is related to baseline PSA level. However, in this age group, death from prostate cancer was infrequent compared to other causes, even when baseline PSA was markedly elevated (up to 20.0ng/ml). A conservative approach to invasive investigation may be appropriate in men older than 65 years.

6. A randomised interventional trial of omega-3-polyunsaturated fatty acids on endothelial function and disease activity in systemic lupus erythematosus.

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Objective: To determine the clinical effect of dietary supplementation with low dose omega-3-polyunsaturated fatty

acids on disease activity and endothelial function in patients with systemic lupus erythematosus.

Methods: A 24 week randomised double-blind placebo-controlled parallel trial of the effect of 3g of omega-3-polyunsaturated fatty acids on 60 patients with SLE was performed. Serial measurements of disease activity using the revised Systemic Lupus Activity Measure (SLAM-R) and British Isles Lupus Assessment Group index of disease activity for SLE (BILAG), endothelial function using flow mediated dilation of the brachial artery (FMD), oxidative stress using platelet 8-isoprostanes and analysis of platelet membrane fatty acids were taken at baseline, 12 and 24 weeks.

Results: In the fish oil group there was a significant improvement at 24 weeks in SLAM-R (from 9.4±3.0 to 6.3±2.5, p<0.001); in BILAG (from 13.6±6.0 to 6.7±3.8, p<0.001); in FMD (from 3.0% (-0.5-8.2) to 8.9% (1.3-16.9), p<0.001) and in platelet 8-isoprostanes (from 177pg/mg protein (23 – 387) to 90 pg/mg protein (32 – 182), p = 0.007).

Conclusions: Low dose dietary supplementation with omega-3 fish oils in SLE not only has a therapeutic effect on disease activity but also improves endothelial function and reduces oxidative stress and may therefore confer cardiovascular benefits.

7. The systemic effects of cilostazol on exercise-induced lower limb ischaemia-reperfusion in patients with peripheral arterial disease.

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Objectives: The phosphodiesterase-3 inhibitor Cilostazol improves walking distance in peripheral arterial disease

Absolute rate of cancer / 1000 person years (Hazard Ratio*)

PSA level	65 - 69	70 - 75	75 - 79	≥80	Prostate specific mortality [†]	All cause mortality [†]
0.0-1.99	0.8 (1.0)	1.2 (1.0)	1.5 (1.0)	2.3 (1.0)	0.3 (1.0)	57.7 (1.0)
2.0-3.99	3.2 (3.8)	2.3 (1.9)	2.6 (1.8)	4.4 (1.9)	0.6 (2.3)	61.3 (1.0)
4.0-5.99	7.7 (9.2)	5.7 (4.7)	4.0 (2.7)	5.6 (2.5)	1.1 (3.8)	60.3 (1.0)
6.0-7.99	12.8 (15.3)	10.9 (8.9)	9.8 (6.6)	9.2 (4.0)	1.8 (6.4)	65.0 (1.0)
8.0-9.99	20.1 (23.8)	16.5 (13.4)	10.2 (6.9)	11.2 (5.0)	3.3 (11.8)	64.2 (1.0)
10.0-14.99	22.6 (26.7)	29.1 (23.1)	21.1 (14.0)	15.6 (6.6)	3.9 (13.5)	76.2 (1.1)
15.0-19.99	44.2 (51.3)	37.0 (28.9)	36.3 (23.4)	35.8 (14.6)	8.4 (28.6)	86.6 (1.2)
≥20.0	105.1 (115.2)	107.0 (79.1)	131.6 (77.2)	115.2 (45.8)	34.0 (112.8)	112.9 (1.5)
No. of cancers	476	580	509	588	673	13074
No. of patients	9933	9884	7978	8154	36003	36003

*0.0 - 1.99 used as reference category, [†]All men, age-adjusted

(PAD) patients through an increase in cyclic AMP levels. The study objective was to assess the effects of cilostazol on the inflammatory response post-exercise in such patients.

Methods: PAD patients were prospectively recruited to a randomised double-blinded, placebo-controlled trial. Baseline clinical data were recorded following medical optimisation. Initial and absolute walking distances were measured on a validated treadmill protocol. Inflammatory response was assessed before and 30-minutes post-exercise by serum lipid hydroperoxide, interleukins 6 and 10, intracellular and vascular cell-adhesion-molecules (I-CAM & V-CAM), highly-selective C-reactive protein (hsCRP) measurement and plasma ascorbate analysis. All tests were at baseline, 6-weeks and 6-months.

Results: 106 PAD patients (72 males) were recruited from August 2004 to August 2006 (overall median age: 66.5, range 37-86). 26 patients were diabetic. Treatment limbs were demographically and medically matched. Patients who received cilostazol, compared to placebo, demonstrated a mean percentage improvement from baseline in absolute claudication distance (77.2% vs. 26.6% at 6 weeks and 161.7% vs. 79.0% at 6 months, $p < 0.05$, t-test). There was a reduction from baseline lipid hydroperoxide levels in the cilostazol group compared to an increase in the placebo group before and after exercise (6-weeks: pre-exercise: -11.8% vs. +5.8% and post-exercise: -12.3% vs. +13.9%) (6-months: pre-exercise -15.5% vs. +12.0% and post-exercise: -9.2% vs. +1.9%) ($p < 0.01$, MWU-test). Cilostazol significantly reduced I-CAM and V-CAM levels at 24-weeks compared to baseline ($p < 0.05$, WSR-test). However, there was no difference between groups for interleukins 6 and 10, ascorbate or hsCRP levels.

Conclusions: Cilostazol is a highly efficacious treatment for improving walking distance in patients with PAD with additional beneficial effects on lower limb ischaemia-reperfusion both before and after walking.

B. POSTER PRESENTATION CASE REPORTS

1. Vasoactive intestinal polypeptide secreting pancreatic tumour (VIPoma): long term survival after orthotopic liver transplantation.

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A 46 year old male presented in 1981 with a two year history of profuse watery diarrhoea, three stone weight loss and fatigue. On examination he appeared gaunt with diffuse muscle weakness. Investigations revealed hypokalaemia (2.5mmol/L; NR 3.5-4.5), achlorhydria and a raised vasoactive intestinal polypeptide (VIP) (1500ng/L; NR 0-100). Abdominal CT showed a 5 cm pancreatic mass but with no focal liver pathology. A distal pancreatectomy was performed. Histology confirmed an islet cell carcinoma (VIPoma).

His symptoms recurred one year post surgery, at which time liver metastases were demonstrated radiologically.

He responded initially to three courses of Streptozotocin but ultimately developed resistance. For fifteen years his symptoms were controlled by octreotide injections, initially Sandostatin (subcutaneously) and later Sandostatin LAR. The patient also underwent hepatic chemoembolisation.

By 1997, sixteen years after his initial surgery, treatment failure occurred with a profound deterioration clinically and debilitating diarrhoea. No evidence of extra hepatic disease was found. After extensive discussion he underwent orthotopic liver transplantation which resulted in resolution of his symptoms.

Recurrence was noted two years post transplant in the para-aortic lymph nodes but not in the liver. He remained mildly symptomatic with gradual deterioration of his general health and died 9 years after liver transplantation.

This case is one of the longest reported (25 years) survivors of a VIPoma after initial diagnosis. The case also has several notable features including the absence of liver metastases at diagnosis and the variety of treatment modalities used for symptom control including successful orthotopic liver transplantation.

2. Opsoclonus Myoclonus Syndrome as a paraneoplastic manifestation of benign ovarian teratoma

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The Opsoclonus Myoclonus Syndrome (OMS) is characterised by nonrhythmic involuntary ocular oscillations, axial and segmentary myoclonia and cerebellar ataxia. It can be a post-infectious, paraneoplastic or idiopathic phenomenon; most commonly associated with neuroblastoma in children and lung or ovarian malignancies in adults. We report the case of a fifteen-year-old girl who presented with subacute onset of opsoclonus and myoclonus, ataxia, nausea and vomiting. Investigation excluded infection, neuroblastoma, chest and breast malignancy but revealed a right-sided benign ovarian teratoma. Paraneoplastic and atypical antibodies including antibodies to neuronal surface antigens and NMDAR antigens were not identified and tumour markers were normal.

The patient was treated with immunomodulatory treatment including intravenous steroids and immunoglobulin but showed the most improvement in response to surgical removal of the teratoma. We discuss OMS as a paraneoplastic manifestation of benign ovarian teratoma. Case reports have suggested a variety of neurological paraneoplastic syndromes associated with this tumour but its association with OMS has not previously been described. We have video evidence pre and post treatment.

3. Macroprolactinomas presenting as nasal polyps: a series of three cases.

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Intranasal presentations of pituitary tumours are rare. Management can be difficult and delayed due to their location and extension. Macroprolactinomas are uncommon and can

often pursue an aggressive clinical course, including invasion into the nasopharynx.

We describe three cases of prolactinomas that initially presented to the ENT Department as nasal polyps. We describe their clinical features and response to treatment. Recurrence of nasal polyps (patient 1) and radiological evidence of a pituitary mass (patients 2 & 3) prompted testing for a prolactinoma. None of the patients had any signs of hyperprolactinaemia. All have significant residual tumour at follow up, despite prolactin levels approaching the normal range on dopaminergic therapy.

Pituitary tumours that invade the nasal cavity are rare and clinicians should be aware of their existence. Measurement of serum prolactin and immuno-histochemistry for prolactin secreting cells in intranasal tumours should be considered if there is clinical evidence of hyperprolactinaemia or if there is recurrence of the nasal tumour/polyp. This can expedite a diagnosis and prevent delay of treatment with dopamine agonists. Dopaminergic therapy controls excessive prolactin secretion and results in tumour shrinkage in most patients, but treatment may be complicated by dopamine resistance, extensive tumour necrosis and CSF rhinorrhoea.

4. Atypical Addison's Disease. -A case of Familial Glucocorticoid Deficiency.

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A 2 yr old boy presented initially with hypoglycaemia following a 6h fast prior to an elective surgical procedure. Investigations demonstrated low plasma glucose (1.6mmol/l),

undetectable serum insulin, elevated beta hydroxybutyrate (5.2mmol/l) and normal lactate. Plasma amino-acid profile was normal. The dorsum of his hands were pigmented, however a synacthen test demonstrated a normal cortisol response. Ketotic hypoglycaemia was diagnosed, and his parents were given dietary advice. At age 11, he was referred to medical genetics with poor coordination, delayed fine motor skills and a dysmorphic appearance. Chromosomal analysis revealed a normal male karyotype, and no specific diagnosis was made.

He presented at age 18 to our unit with recurrent hypoglycaemia. A 72h fast was terminated after 10 h as the patient was symptomatic with plasma glucose 1.6mmol/l. A synacthen test demonstrated an absent cortisol response and elevated ACTH level. Serum electrolytes were normal, adrenal autoantibodies were absent and very long chain fatty acids were normal. He was commenced on both glucocorticoid and mineralocorticoid replacement and had no further hypoglycaemic episodes.

Later the patient's brother also presented at age 16 with hypoglycaemia when he was unwell with nausea and vomiting. A diagnosis of primary adrenal insufficiency was confirmed - also with normal serum electrolytes and absent adrenal autoantibodies.

Further genetic analysis revealed that both brothers were homozygous for the S74I mutation of the MC2 (melanocortin 2) receptor and a diagnosis of Familial Glucocorticoid Deficiency (FGD) was made. This rare autosomal recessive ACTH insensitivity syndrome responds to glucocorticoid replacement alone.