Lipoprotein apheresis was commenced in June 2012. Treatment is carried out via native veins bi-weekly using the Kaneka DHP DX21 whole blood system. This has resulted in an average reduction of 50.10% in TC, 52.97% in LDL and 55.91% in Lp(a). The plan is to increase the volume of blood treated at each session but he is unable to sit still for long enough to achieve this due to the xanthoma on his buttocks. He has been referred for urgent surgery on these lesions. Regular lipoprotein apheresis will hopefully further reduce the cholesterol level and xanthomata. However issues other than venous access can affect the ability to achieve optimum results.

SMITH-LEMLI-OPITZ SYNDROME, CAUSED BY DEFICIENCY IN THE LAST STEP OF CHOLESTEROL BIOSYNTHESIS: THE BRISTOL UKTN DHCR7 MUTATION SERVICE

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Cholesterol is produced from lanosterol through a series of reactions in the post-squalene cholesterol pathway. Several human malformation syndromes are caused by defects at different points in the pathway resulting in deficiency of cholesterol and accumulation of precursors: Smith-Lemli-Opitz (SLOS), Lathosterolosis, Desmosterolosis, CDPX2, CHILD syndrome, SC4MOL, and Antley-Bixler.

SLOS is an autosomal recessive disorder caused by a deficiency of 7-dehydrocholesterol reductase (DHCR7) in the last step of cholesterol biosynthesis, resulting in low cholesterol and raised 7-Dehydrocholesterol (7-DHC) levels. The phenotype ranges from intrauterine lethality through to mild dysmorphism/mental impairment with a carrier frequency of <7-DHC) levels. The phenotype ranges from intrauterine lethality through to mild dysmorphism/mental impairment with a carrier frequency of 3% in Caucasians. A combination of cholesterol deficiency and toxic effects of 7-DHC or derivatives is thought to cause the SLOS phenotype by affecting: structural lipids of membranes, steroid hormones, neuroactive steroids, oxysterols, bile acids and maturation of the embryonic signalling hedgehog family of morphogens.

Biochemical services have been offered since 1995, however, results can be equivocal, carrier testing is challenging and not readily available in the UK. A UKTN DHCR7 mutation analysis service was introduced in 2009 for: 1) diagnosis in biochemically equivocal normal cases with a SLOS phenotype, 2) retrospective carrier testing of parents where no proband material remains, 3) cascade carrier testing.

DHCR7 screening by sequencing (ABI3730) has detected 26 different pathogenic mutations (including 2 novel point mutations and a novel large intragenic deletion) in 31 clinically/biochemically affected cases with subsequent carrier status confirmation for 20 couples. 10 parents were found to be carriers where the foetus or deceased child had not been tested. 14 patients with family history and 6 population risk partners have also been tested.

We present the clinical and mutation data of the broad phenotypic range of patients tested to demonstrate the utility of the DHCR7 mutation service in facilitating diagnosis, identification of carriers, and possible genotype-phenotype correlations.

IDENTIFICATION OF FAMILIAL HYPERCHOLESTEROLAEMIA WITHIN PRIMARY CARE – A COLLABORATIVE APPROACH WITH COMMUNITY GP NETWORKS

D Townsend, Edmunds L, Gingell R, Edwards R, Datta BN are part of the Welsh FH Team. K Haralambos is a Research Officer, Welsh FH Project A Cookson, A Gunneberg and N Haboubi are Consultant Chemical Pathologists in SW Wales. I O Connor is a GP Community Network Lead, Bridgend.

Heterozygous familial hypercholesterolaemia (FH) is a genetic condition that predisposes individuals to premature cardiovascular disease with an estimated frequency of 1 in 500 of the population. Currently within the United Kingdom only 25 per cent of the 110,000 individuals affected by this condition are diagnosed. The All Wales FH service was commenced in September 2010 and provides access to FH genotyping and is closely affiliated to lipid clinics within secondary care. We have introduced a number of initiatives with colleagues in primary care, to help identify individuals with possible FH in the community.

Within the Borough of Bridgend in South Wales, there are three community networks divided (East, West and North) each of which incorporates several GP Practices. As a result of several meetings and presentations with the Community Medical Director, the community network lead and the FH multidisciplinary team, it was agreed that FH primary care clinics could be initiated.

Primary care database searches were carried out and potential patients identified. Following assessment of suitability by the FH nurse and practice staff, suitable patients were invited to attend their local medical centre for assessment of FH and suitability for genotyping for FH. To date seven of the ten surgeries are taking part with a total population size of 83,336. Two practices have been completed with clinics currently ongoing in a third.

PATTERNS AND ASSOCIATIONS OF LOW DENSITY LIPOPROTEIN DURING AND AFTER PREGNANCY IN A SOUTHERN AFRICAN POPULATION

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Small low-density lipoprotein (LDL) is atherogenic and is associated e.g. with hypertriglyceridaemia, obesity, metabolic syndrome and diabetes mellitus. This fraction has been reported in pregnancy hence this study investigated the prevalence of various species of LDL in pregnancy and the association of LDL species with plasma triglyceride concentration and apolipoprotein E genotype.

Four hundred and seventy two non-diabetic women were studied at antenatal clinics in Harare, after obtaining informed consent. Blood was taken during pregnancy (between 13-36 weeks) and at least 6 weeks after delivery. Enzymatic spectrophotometric methods were employed to measure plasma triglyceride, cholesterol, high-density lipoprotein cholesterol concentrations and LDL cholesterol was calculated. Non-denaturing gradient gel electrophoresis was employed to classify LDL species into 5 categories: A, AI, IB and B in decreasing sizes and genotyping of apolipoprotein E (apoE) genotype.

Statistical analyses were carried out by non-parametric t-tests and contingency tables; significance was taken as p<0.05. Four hundred and seventy two subjects were analysed before and after pregnancy. The median plasma triglyceride concentration was significantly higher in pregnancy: medians of 1.5 and 0.6 mmol/L, with 95% confidence intervals of 1.5 to 2.2 and 0.6 and 0.7 mmol/L, respectively, p<0.0001. Total cholesterol (mmol/L) was also significantly higher during pregnancy, 4.1 median (4.1-4.3 95% confidence interval) and 3.6 (3.5-3.6), p<0.0001. The median LDL cholesterol concentration (mmol/L) did not change significantly (2.0, 2.0-2.1). Antenatally, 6% of the patients had no clearly definable LDL species, while 3% had 2 species of LDL and the remainder had a single species. During postpartum dual species were seen in 2%. The distribution of the LDL species antenatally in the categories A, AI, IB, B was 2, 9, 35, 46 and 10, respectively. The % LDL sp postpartum distribution was: 44, 26, 26, 3 and 1, respectively χ2 test p<0.0001.

Pregnancy may precipitate significant hypertriglyceridaemia in susceptible individuals. The mild hypertriglyceridaemia of pregnancy is associated with smaller LDL particle size. Lipid profiles need to be monitored during and after pregnancy in such patients.
Familial Hypercholesterolaemia Genetic Search Strategy

All patients with an LDL > 6.5mmol/l, excluding those with a triglyceride of >2.5mmol/l
Consider those who fulfill Simon Broome Criteria with a personal history of CVD < 60 years
Additional search strategies:
- High dose statins +/- ezetimibe: Total cholesterol > 8 mmol/l
- Exclude secondary causes of hypercholesterolaemia
- These individuals may be suitable for genetic testing

This has negated the need for initial referral to secondary care to access genotyping and had a subsequent impact on waiting time for new patients into lipid clinic.

LIPOPROTEIN APHERESIS – THE CARDIFF EXPERIENCE

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Introduction: Cardiff Lipid Unit has performed lipoprotein apheresis for 22 years and has completed over 6000 treatments. The unit has 18 patients and utilizes 4 different lipoprotein apheresis techniques. We assessed our treatment efficacy against published standards for 2012 as follows, LDL (low density lipoprotein) cholesterol reductions following treatment of 60%* with a post treatment LDL of <1.8mmols/l, total cholesterol (TC) reduction of 50% and lipoprotein(a) (Lp(a)) reduction of 50%.(Thompson et al 2010) A database was created to facilitate data collection and analysis

Method: During 2012 Cardiff Lipid Unit performed 432 lipoprotein apheresis treatments in 18 patients. Each patient received apheresis treatments once per fortnight. Blood samples were taken before and after each treatment and the results were collated. Percentage reduction and mean total and LDL cholesterol values were calculated and averaged over the course of the year for each patient and thereafter for the whole unit.

Results: Unit averaged data were as follows. Mean post treatment LDL cholesterol values of 1.55mmol/l with a reduction of 67%, Lp(a) reduction of 66% and TC reductions of 55%

Conclusion: Analysis of data from the database demonstrates that all efficacy targets were met following lipoprotein apheresis treatment. Periodic analysis of data ensures that targets are met with the aim of optimising cardiovascular outcomes.

EXTENDED RELEASE NIACIN LOWERS MEDIATORS OF VASCULAR INFLAMMATION BUT DOES NOT IMPROVE IN VITRO HDL ANTIOXIDANT FUNCTION IN STATIN TREATED DYSLIPIDEMIC PATIENTS

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Aims: Several randomised controlled trials have previously examined the effects of extended release niacin/laropiprant (ERN/LRP) combined with low dose statins in dyslipidaemic patients. I investigated the influence of ERN/LRP versus placebo in patients who had persistent dyslipidaemia despite receiving high doses of potent statins as the latter more accurately reflected actual clinical practice. I assessed the effect of ERN/LRP on mediators of vascular inflammation and HDL’s in vitro anti-oxidant function.

Methods: This was a randomised double blind cross over trial. I studied the effect of ERN/LRP compared to placebo in 27 patients who were receiving maximum tolerated doses of statins and gauged compliance. I measured lipid profile, apolipoproteins, cholesteryl ester transport protein (CETP) activity, glycerated apolipoprotein B100 (gly apoB), paraoxonase 1 activity (PON1), oxidised LDL (oxLDL), lipoprotein phospholipase A2 (Lp-PLA2), lysophosphatidyl choline (lyso-PC), macrophage chemoattractant protein (MCP1), serum amyloid A (SAA) and myeloperoxidase (MPO). I also examined the capacity of HDL to protect LDL from oxidation.

Results: ERN/LRP treatment was associated with a significant improvement in HDL cholesterol and significant reduction in total cholesterol, triglycerides, LDL cholesterol, non-HDL-C, total apoB, lipoprotein (a), CETP activity, oxLDL, Lp-PLA2, lyso-PC, MCP1 and SAA. HDL’s capacity to protect LDL against in vitro oxidation did not improve on treatment with ERN/LRP compared with placebo.

Conclusions: Treatment with ERN/LRP results in a significant improvement in HDL-C and reduction in pro-atherogenic lipoproteins/apolipoproteins in patients who have persistent dyslipidaemia despite high doses of potent statins. For the first time I have shown that ERN/LRP reduces mediators of vascular inflammation but does not affect HDL’s in vitro anti-oxidant function in these patients. Withdrawal rates due to flushing were 5% as a result of combining laropiprant with niacin.