FH PAEDIATRIC REGISTER NEWSLETTER

THE NEWSLETTER FOR CLINICIANS WHO ARE REGISTERED WITH THE FAMILIAL HYPERCHOLESTEROLAEMIA PAEDIATRIC REGISTER WEBSITE

Latest Numbers

There are now 197 patients enrolled into the database, an increase of nearly 40 since the start of 2014. Of the 29 patients enrolled from before May 2013, 21 patients have had follow up information from a later clinic date entered into the system.

Database Updates – Coming Soon!

As the database is being heavily used by individuals registering and enrolling their patients, a number of potential improvements have been identified. We hope that by making these updates, the system will be more user-friendly for you! Some of the improvements have already been made, and others are planned:

- Date (year) restrictions removed – so any 'reasonable' dates can be entered
- Reference ranges made clinically relevant
- Acceptance of '>' symbol in genomic nomenclature/family mutation box
- Addition of decimal places for height
- Consistency of error message text
- Help boxes cleaned up

We welcome your feedback on these database changes, plus any other suggestions you have for improving data entry into the system.

LIGHTS, CAMERA….!

A long-awaited video to provide information about FH to children and their families is almost here! We intend to make this video available electronically to all registered clinicians on the website, so that you can share the video with your patients and their families.

We will send you the link once it is available for use.

STOP PRESS

FH hit the BBC headlines in May with the news that genetic testing for heart disease is to be rolled out later this year:

http://www.bbc.co.uk/news/health-27586009

Upcoming Events and Publicity

HEART UK Conference
2-4th July, Warwick University

Steve will be presenting, and if you would be interested in attending his lunch workshop session, please let us know: fh@rcplondon.ac.uk

BIMDG Annual Meeting
19th and 20th June, Stirling
http://www.bimdg.org.uk/symposium/poster.asp

Articles about the Register were featured in the Feb/March edition of 'Cardiology News' and in the RCP Presidents Bulletin in December 2013

The RCPCH Conference—summaries overleaf

8-10th April 2014, Birmingham

Uma's workshop was a success, being attended by over 40 delegates. Three new physicians registered directly after the meeting and a number more took away leaflets. Several interested delegated also stayed behind after the workshop to ask Uma and the other speakers further questions. The workshop demonstrated a general feeling of motivation for colleagues within lipid clinics to work together in order to coordinate the screening and identification of children with FH, so that they can be receive treatment earlier. **Please find the Summary Presentations on the next page.**

At the same conference, Uma also presented the data at the BIMDG session & chaired a workshop which was well attended with over 60 delegates.

Update on DNA testing in BHF Cardiovascular Genetics at UCL—a note from Steve Humphries

I am pleased to tell you that over the last few months we have received more than 30 blood or DNA samples from clinicians with children whose data has been entered onto the Register, but where the family mutation is yet unknown (or yet to be tested for). An *LDLR* FH causing mutation has been found in 16 of these samples, and the clinicians informed. In 8 samples the screening has been completed (including MLPA to look for gross deletions or insertions) and no mutation has been identified, and in the remainder analysis is still on-going. Overall we have therefore identified the family mutation in 67% of the samples which is very encouraging. We are happy to continue to offer this free service to any clinicians involved in the Register and please see the Register website for the informed consent form and proforma that needs to accompany every submitted sample

Royal College of Physicians

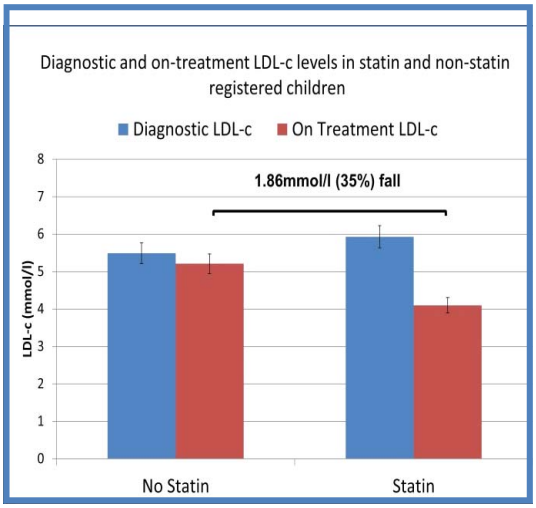
Please click here for more information about registering

FH Paediatric Register

RCPCH Royal College of Paediatrics and Child Health

RCPCH Conference—Presentation Summaries

At the Birmingham RCPCH meeting we were able to present an up to date analysis from the 150 children where we have complete register data. Of particular interest was the number of children being treated with a statin and the characteristics of this group, to see if appropriate clinical judgement was being used in recommending statin treatment. Overall, 59% of the children are being treated with statin and the mean age of this group was significantly higher than in the no statin group (13.8 v 11.9 years, p = 0.0005). There was no evidence of a difference in statin treatment in boys and girls but as expected a significantly higher proportion of the treated group had evidence of CHD in a parent (31% v 16% p = 0.04) or CHD in a relative (51% v 34% p = 0.05). At diagnosis the mean LDL cholesterol levels of the group who ended up on statin treatment was marginally higher (5.93 mmol/L v 5.49 mmol/L, p= 0.09) and of course the on-treatment LDL cholesterol level in the treated group but not the non-treated group had fallen significantly as shown in the accompanying histogram. Overall this indicates that appropriate clinical judgement is being used by the treating physicians, and we intend to start preparing this very valuable data for publication in the next few months.



Dr Uma Ramaswami

Consultant Metabolic Paediatrician

Royal Free Hospital

How to save lives in children with Familial Hypercholesterolemia?

In the study of early atherogenesis, children with familial hypercholesterolemia proved to be an excellent model for the elucidation of important risk factors. We in fact studied this question in more than 1000 children. To conclude, in FH families, LDL-c levels (>3.5 mmol/L) allow accurate diagnosis of FH in childhood, and moreover, increased LDL-c (>6.23 mmol/L) and lipoprotein(a) (>300 mg/l) and decreased HDL-c levels (<1.0 mmol/L) in children identify FH kindred with the highest CAD risk. (Wiegman e.a. Circulation 2003, 107:1473-1478)

Patients with FH suffer from severe CAD early in life. Should lipid-lowering treatment started in childhood? We therefore assessed 201 children heterozygous for FH and 80 unaffected siblings (both age ranges 8–18 years) with ultrasound to measure carotid wall intima-media thickness. Mean carotid IMT of heterozygotes was significantly greater than that of unaffected siblings. A significant deviation in IMT was noted before age 12 years. LDL-c, age, and sex showed to be strong and independent predictors of IMT. Since raised LDL-c can be lowered efficiently, studies were needed to investigate long-term safety and effectiveness of statin treatment in children with FH. (Wiegman e.a. Lancet 2004, 363:369-370)
Would early intervention with pravastatin inhibit the process? Treating 214 children with FH (aged 8 to 18 years) in a randomized, double-blind, placebo-controlled, two-year trial with pravastatin 20-40 mg, compared to baseline, carotid IMT showed regression on pravastatin and progression in the placebo group. The change of IMT between the two groups differed significantly. No differences were observed for growth or maturation between both groups. So, early intervention with pravastatin is efficacious, safe and therefore probably desirable. (Wiegman e.a. JAMA 2004, 292:331-337)
Five-year mean follow-up of the long term pravastatin study was in fact 4.7 years and statin-use proved to be effective and safe. The age at which statins were introduced in children was a significant independent predictor on cIMT. Earlier initiation of statins will prevent premature atherosclerosis. (Rodenburg e.a. Circulation 2007, 116:664-668)

Ten-year follow-up was achieved in 90% of subjects. Mean (±standard deviation) low-density lipoprotein cholesterol levels were still higher in FH subjects than in their siblings (173±66 versus 124±32 mg/dL; *P*<0.001). Mean carotid intima-media thickness (c-IMT) was also slightly, but significantly greater in FH patients (0.480±0.058 versus 0.469±0.050 mm; *P*=0.015) (Fig. S2, Supplementary Appendix), but mean c-IMT progression was similar in both groups (0.039±0.051 versus 0.037±0.045 mm; *P*=0.52). These data indicate attenuated progression of c-IMT in statin treated FH children and might predict a reduction of coronary events later in life. (unpublished data)

Currently, twenty-six children on pravastatin exceed the age their affected parent suffered their first myocardial infarction or died.

A.Wiegman, MD, PhD

Paediatric Cardiologist

Familial Hypercholesterolaemia - pathophysiology and genetics

Familial Hypercholesterolemia (FH) is an autosomal dominant disorder affecting LDL-cholesterol (LDL-C) metabolism. Its frequency ranges from as high as 1/70 in countries where there is a founder gene effect, for example South Africa, to ~ 1/500 in most countries where there is marked genetic heterogeneity, although a recent report from Denmark found a frequency of ~ 1/200. The clinical diagnosis of FH is based on algorithms developed in different populations: the UK's Simon Broome criteria, the Dutch lipid clinic score, and the American MEDPED criteria, which are essentially based on total cholesterol levels above ~7.5mmol/l or more specifically LDL cholesterol >~5mmol/l, the presence of tendon xanthomas as a sign of long term cholesterol elevation, and evidence of a familial history of early CHD or hypercholesterolemia. The first gene identified where mutations cause FH was the LDL receptor (LDLR), and there are now more than 1200 different LDLR defects reported in FH patients world-wide. However mutations in genes coding for proteins that interact with the LDL receptor can also cause the FH phenotype, with the second most common cause being a single mutation in APOB, encoding apolipoprotein B, the major ligand for the LDL-R. Using a linkage approach the third FH gene was identified as PCSK9, encoding proprotein convertase subtilisin/kexin type 9 a protein involved in controlling the recycling of the LDL-R, where gain-of-function mutations cause FH. Finally again using a linkage approach the LDLRAP1 gene was identified, which encodes an adaptor protein which is involved in correctly anchoring the LDL-R in the clathrin coated pit for endocytosis, and here the inheritance pattern is recessive, showing that having half normal levels of this protein is compatible with normal levels of LDL-C.

Overall, ~60% of patients with a clinical diagnosis of possible or definite FH phenotype are mutation-negative by conventional testing. We evaluated the hypothesis that the FH phenotype can be reproduced by an accumulation of common small-effect LDL-C raising alleles (Talmud et al., Lancet 2013). We used a weighted LDL-C-raising gene score based on 12 common LDL-C raising alleles documented by Genome Wide Association studies. The results strongly suggest that a substantial proportion of FH patients with no identified mutation (at least 20% and possible up to 60%) are likely to have a polygenic cause of the elevation in LDL-C rather than an as yet unidentified single gene mutation. Cascade testing would be less effective in such cases, since the number of them inheriting this high number of LDL-raising SNPs would be considerably lower than the 50% affected relatives expected for monogenic inheritance. We propose that patients with an FH phenotype, where no FH-causing mutation can be found, should be given the clinical diagnosis of polygenic hypercholesterolaemia, and not Familial Hypercholesterolaemia. This should not, however, affect the treatment of these patients, but would influence the decision to conduct cascade testing in their relatives

Marta Futema, PhD on behalf of Prof Steve Humphries

UCL, Institute of Cardiovascular Sciences, Department for Cardiovascular Genetics

Familial Hypercholesterolaemia Cascade Testing – The Welsh Experience

It is recognised that at least 1 in 500 children in the UK will have Familial Hypercholesterolaemia (FH). It is essential that children with FH are identified before they reach late adolescence or adult life, and treatment commenced to avoid the increased risks of untreated young adults dying of coronary heart disease.

It is unusual for a child to present to a paediatric clinic with high cholesterol levels (other than recognised conditions such as hypothyroidism, nephrotic syndrome etc) as a potential index case of FH and therefore high quality family cascade testing is essential in order to recognise children at risk of this condition.

For over 5 years Wales has been offering family FH testing through the All Wales FH Cascade Testing Service which has led the way on FH services in the UK. Cascade testing will be available in England later this year.

Following the recognition of an index case of FH (almost exclusively an adult) an accurate family history is obtained, genotype testing undertaken and if genotype positive the family is introduced into the All Wales FH Cascade Testing Service by FH Specialist Nurses who link with genetic counsellors to offer genetic testing for all first degree relatives. This requires close joint working between the FH Specialist Nurses and the Genetic Department. The information about family members and results of genotyping are available on our PASS Clinical FH Cascade Software which can be seen by those involved in the diagnosis of a patient with FH.

Following the family pedigree being established and those patients at risk of FH recognised, we have been surprised that a number of families have been reluctant to contact the FH service for genetic testing with the associated risk that children with possible FH may not be recognised. We have learnt that the rapport between FH Nurses and FH index patients is important to encourage genetic testing for family members.

In order to achieve NICE Quality Standard Four, children at risk of FH being offered diagnostic testing by the age of 10 years and Quality Standard Seven of children being assessed for lipid modifying drug therapy in a child appropriate setting by the age of 10 years FH Cascade testing is essential.

It is extremely important that every family in whom the FH gene has been recognised should participate in cascade testing so that their children and grandchildren have the best chance of growing up to be healthy young adults without increased risks of cardiovascular disease.

Dr Peter Dale

Consultant in Paediatrics

Aneurin Bevan UHB - Paediatrics