FH PAEDIATRIC REGISTER NEWSLETTER

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

BHF Funded Nurses

We are pleased to tell you that there are now a whole group of BHF funded nurses in 11 different centres throughout the UK who will be doing cascade testing from FH patients with a known mutation. The result of this, of course, is that they will be finding a lot of new children with FH, and part of their job description is to enter the information about these children onto the FH Register. We had a Training Day for the nurses just before Christmas and as you can see from the photo below they are a very enthusiastic and happy group! Both Uma, Mary Seed and I presented a series of lectures to the nurses covering all aspects of the identification and management of both adults and children with FH, and of course about the molecular genetics. They were also given extensive training from Kate Haralambos about how to use the PASS pedigree drawing and database management software. We are very hopeful that we may be able to download quite a lot of the Register information directly from the PASS database which would make everyone's life much easier, and also reduce any data entry errors. The BHF have recently announced the possibility of funding for additional nurses so hopefully their numbers will increase over the next couple of months.

FH is a family affair –A reminder from Dr Peter Dale (Paediatrician)

Family cascade testing from parents and grandparents who have an FH gene is important so that children and young people who inherit the gene can be recognised early and offered treatment when appropriate. Genetic testing in children is very easily carried out by either blood or saliva samples when the family gene is known. We recommend that children are genetically tested from the age of eight years and offered treatment by the age of 10. Every family should participate in cascade testing so that their children and grandchildren have the best chance of growing up to be healthy young adults without the increased risks of cardiovascular disease.

Database Updates—Annual reminders

You may have noticed that the register has been upgraded to send auto-reminders once your patient has been on the system for over a year, asking you to complete the annual update form.

If you have any questions or would like to give us any feedback on how we could improve the register, then please email fh@rcplondon.ac.uk

LATEST FIGURES

There are currently 250 children enrolled compared with 221 at last meeting (Sept 2014).

To date: 57 Groups (Trusts) and 77 clinicians have registered on the system to enrol patients.

27 Hospitals have entered data. (1 new site has registered patients – Royal Free)

Top recruiting site is the Royal Brompton with 31 patients.

Royal College of Physicians

Please click here for more information about registering

FH Paediatric Register

RCPCH Royal College of Paediatrics and Child Health

FH Steering Group

The register is overseen by 2 groups, the Executive Committee and the Steering group. The Executive Committee is responsible for the management and good governance of the project . The Steering Group, is responsible for the strategic and clinical direction of the project . They are both chaired by Prof Humphries.

There have been some new members to the Steering Group, our new patient representative, Mr Mark Fisher, and a new BHF funded FH cascade nurse, Ms Lorraine Priestley-Barnham.

Our new patient representative, Mr Mark Fisher

I was invited to join the steering group by Dr Mary Seed who I was referred to aged 18 having suffered palpitations whilst skiing. Both my children, who are now 18 and 16 have been diagnosed with FH, so I hope to bring some experience and understanding of what it is like for children growing up with FH.

I am a Father, Son and at least Grandson to FH patients. My Grandfather died from CHD aged sixty and my Father suffered his first heart attack at the age of 35 and has since had two multiple bypass operations, stents and last year a valve replacement.

It has been an interesting journey experiencing the advances in knowledge and treatment of FH over the past 30 years. My Granddad was unaware of the condition and my Father's treatment following his heart attack was to stop smoking and change his diet, this progressed to fortnightly LDL Apheresis sessions, which together with ongoing surgery have enabled him to live to beyond retirement age, something which was not envisaged at the time of his diagnosis.

Personally, I have been in the capable hands of Dr Mary Seed for the last 28 years. I was diagnosed at a relatively young age and treated with statins and advised on diet and healthy lifestyle choices. I have had hiccups along the way but I am healthy and show no signs of CHD.

When my children were born, their cord blood was tested and unfortunately both showed abnormally high cholesterol levels. A simple DNA test of myself, my Father and two children showed that we all share the same FH gene (as does my sister). The children were referred to GOSH and both started on statins at around 11 years of age. They don't smoke, are aware of their diet and are active and sporty. They are well and as I have proved should continue to be spared the discomfort and suffering of their Grandfather and Great Grandfather - all because of a simple DNA test.

Our New FH Nurse representative Lorraine Priestley-Barnham (pictured above at the far right).

I have recently been recruited as a Clinical Nurse Specialist in FH and Genetic screening at Harefield hospital. My appointment came about as a result of British Heart Foundation funding which also secured the appointment of a number of nurses into genetic screening for FH across the country. The FH genetic screening service at Harefield was established in 2008 under the guidance of Dr Mahmoud Barbir who is a Consultant Cardiologist.

My background is that of paediatrics having completed my nurse training at Great Ormond Street Hospital in 2000. I have spent my entire career in different areas of paediatric cardiorespiratory nursing, I then moved to Harefield where I embarked on the challenges of adult cardiology nursing and nurse led clinics.

I currently work part time and job share my role with Emma Neves who also works part time on the Apheresis unit at Harefield hospital. We are fortunate enough to have Jane Breen as our mentor as we are guided through the very interesting world of FH.

Following our initial 3 month training period, we have now quite literally hit the ground running and between us undertake at least 4 genetic screening clinics per week. Not only do we provide a clinic at our Harefield site, we also attend the Royal Brompton hospital, Hillingdon hospital and a local GP practice.

Our role also requires us to be involved in the follow up of FH patients and each week we take a nurse led clinic which runs alongside the Consultant clinic. In the paediatric outpatient department we also house a family clinic at least 6 times per year where families are seen as a whole unit which encompasses the philosophy of family centred care.

Inspired by our roles, as a team we have set about raising awareness of FH and genetic screening. This has included increasing trust, local and national awareness of the service we offer. We have undertaken clinical education meetings to inform local GP services of the concept of genetic cascade screening for FH and reinforce our referral criteria. A 'flag' system has been set up trust wide on blood results once authorised and local pathology searches have been undertaken with the aim of helping to identify patients who may have FH within the Hillingdon borough.

I was recently invited to join the Paediatric FH steering group and given my paediatric background, I was delighted to accept. As a trust we are very active in registering and recording data for the Paediatric FH register and are very proud of our position as the top recruiting site this year. All physicians involved in the management and care of children with FH are invited to contribute to the Paediatric FH register which was established in 2012. As treatment protocols for paediatric FH patients are varied and flexible depending on family history and medical presentation, this will allow for the collection of baseline statistics and enhance the accuracy of long term follow up data on all children with FH in the UK which will in turn inform and guide future practice.

How common is FH?

We have always used the estimate of the frequency of heterozygous FH of 1 in 500 of the general population. This is based on the extremely rough estimate that about 1 in 1 million live births are homozygous for FH and from this you can work out what the carrier frequency must be. The problem of course is estimating how many homozygous FH patients there are in the UK, given the fact that up until recently so many of them would have died of early atherosclerosis. However, with molecular sequencing now becoming widely available it is possible to get a direct genetic estimate by looking to see how many people from general population samples carry pathogenic mutations in *LDLR* or *APOB* or *PSCK9*. One very interesting recent paper (see below) using this approach in individuals in the US has come up with an estimate of roughly 1 in 200! This very much fits with our unpublished data from the UK 10,000 Genomes Project Humphries and Futema) which also had an estimate in 1 in 250. What this means of course is there are almost twice as many children out there with FH that we need to find through cascade testing and manage in your clinics so there will be plenty of work for everyone!

Do R, Stitziel NO, Won H et al. NHLBI Exome Sequencing Project. Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. Nature 2014;doi:10.1038/nature13917 [Epub ahead of print]
Exome sequencing of 9,793 early MI patients (≤50 years in males and ≤60 years in females) along with MI-free controls. LDLR mutation carriers were at 4.2-fold increased risk for MI; carriers of null alleles at LDLR were at even higher risk (13-fold difference). Approximately 2% of early MI cases harbour a rare, damaging mutation in LDLR; this estimate is similar to one made more than 40 years ago using an analysis of total cholesterol. Among controls, about 1 in 217 carried an LDLR coding-sequence mutation and had plasma LDL cholesterol > 190 mg dl^{-1}.

Articles of Interest.....

Familial Hypercholesterolemia in Greek children and their families: Genotype-to-phenotype correlations and a reconsideration of LDLR mutation spectrum. Mollaki V, Progias P, Drogari E. Atherosclerosis. 2014 Dec;237(2):
LDLR was analyzed in 561 patients from 262 families, by whole-gene sequencing. The spectrum of LDLR mutations in Greece is refined and expanded. Although a quick screening method is feasible for the Greek population, whole-gene sequencing is essential to identify rare variants. Children with border line lipid levels and a family history of hypercholesterolemia should be considered for molecular diagnosis, since carriers of certain mutations show milder phenotypes and may be missed during clinical diagnosis.

Effect of a low-fat diet enriched either with rapeseed oil or sunflower oil on plasma lipoproteins in children and adolescents with familial hypercholesterolaemia. Results of a pilot study. Negele L, Schneider B, Ristl R, Stulnig TM, Willfort-Ehringer A, Helk O, Widhalm K. Eur J Clin Nutr. 2014 Nov 26
While there is convincing evidence that unsaturated fatty acids exert favourable effects on plasma cholesterol levels, it is not clear which type of oil has the most pronounced effect, especially not in paediatric patients. The aim was to compare two low-fat diet regimes enriched with either monounsaturated fatty acids by rapeseed oil (RO) or polyunsaturated fatty acids by sunflower oil (SO) in children affected with FH. Authors concluded that a fat-modified diet enriched with RO seems to have very similar effects on cholesterol levels as with SO. However, our study suggests that RO has possibly more favourable effects concerning cardiovascular risk profile. Both diets appear to be feasible and were well accepted among our subjects.

Statin use in Australian children: a retrospective audit of four pediatric hospitals. Gelissen IC, Nguyen HL, Tiao DK, Ayoub R, Aslani P, Moles R. Paediatr Drugs. 2014 Oct;16(5):417-23.
A retrospective audit of patients prescribed statins during a visit to a pediatric hospital, as in- or outpatients, was performed in four major children's hospitals in three Australian states. A total of 157 patients under the age of 18 were included in the audit. The most common reasons for being prescribed a statin included history of organ transplantation, renal disease and familial hypercholesterolemia (FH). Four statins were prescribed: atorvastatin (n = 77), pravastatin (n = 45), simvastatin (n = 25) and rosuvastatin (n = 10). All statins, apart from rosuvastatin, were used in very young children (1-7 years old). Authors concluded that long-term safety studies on the use of statins in children have only included FH patients so far, who are generally healthy besides their raised lipid levels. Further long-term safety studies are needed to include the more vulnerable transplant and renal patients, identified in this audit as being prescribed statins. This can help formulate guidelines for the safest possible use of this class of drugs in the pediatric setting, including the possibility of weight-based recommendations for younger children.

Dietary interventions (plant sterols, stanols, omega-3 fatty acids, soy protein and dietary fibers) for familial hypercholesterolaemia. Malhotra A, Shafiq N, Arora A, Singh M, Kumar R, Malhotra S. Cochrane Database Syst Rev. 2014 Jun 10;6:CD001918
In this Cochrane Review, only short-term outcomes could be assessed due to the short duration of follow up in the included trials. A significant difference was found for the following comparisons and outcomes: for the comparison between plant sterols and cholesterol-lowering diet (in favour of plant sterols), total cholesterol levels, mean difference 0.30 mmol/l (95% confidence interval 0.12 to 0.48); decreased serum LDL cholesterol, mean difference -0.60 mmol/l (95% CI -0.89 to -0.31). Fasting serum HDL cholesterol levels were elevated, mean difference -0.04 mmol/l (95% CI -0.11 to 0.03) and serum triglyceride concentration was reduced, mean difference -0.03 mmol/l (95% CI -0.15 to -0.09), although these changes were not statistically significant. However large, parallel, randomised controlled trials are needed to investigate the effectiveness of a cholesterol-lowering diet and the addition of omega-3 fatty acids, plant sterols or stanols, soya protein, dietary fibers to a cholesterol-lowering diet.