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Original Article

The UK Paediatric Familial Hypercholesterolaemia Register: Statin-related safety and 1-year growth data

Steve E. Humphries, PhD, FRCP*, Jackie Cooper, MSc, Peter Dale, MBBS, FRCPCH, Uma Ramaswami, MD, on behalf of the FH Paediatric Register Steering Group

Centre for Cardiovascular Genetics, Institute for Cardiovascular Science, University College London, London, UK (Drs Humphries and Cooper); Department of Paediatrics, Royal Gwent Hospital, Newport, Wales (Dr Dale); and Lysosomal Disorders Unit, Royal Free Hospital, London, UK (Dr Ramaswami)

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BACKGROUND: For children with familial hypercholesterolemia (FH), UK guidelines recommend consideration of statin therapy by age 10 years and dietary and lifestyle advice to maintain an ideal body weight.

OBJECTIVES: The objective of the study is to use the UK Paediatric Familial Hypercholesterolemia Register to determine: (1) the prevalence of plasma markers of liver toxicity and muscle damage in statin-treated FH children; (2) the prevalence of obesity in FH children compared to the UK general population; and (3) to compare growth rates in statin-treated and nontreated children.

METHODS: Differences in registration and 1-year characteristics were compared by Mann-Whitney *U* tests. Age and gender body mass index percentiles were compared to UK children's growth charts.

RESULTS: In 300 children (51% boys, 75% Caucasian, untreated mean [standard deviation] low-density lipoprotein cholesterol 5.50 [1.49] mmol/L), the proportion on statins varied significantly ($P < .005$) by age group (<5 years = 0%, 5–10 years = 16.7%, 10–15 years = 57.1%, and >15 years = 73.2%). Statin treatment reduced low-density lipoprotein cholesterol by 31% (1.84 [1.43] mmol/L), and no child showed elevated levels of markers of liver toxicity or muscle damage. At registration, 16.9% of the FH children were overweight (>85th percentile) and 11.1% were obese (>95th percentile) vs reported in 21.2% in UK non-FH children. There was no difference in annual growth rate in statin vs no-statin groups (age-adjusted weight increases 3.58 vs 3.53 kg; $P = .91$, height 4.45 vs 4.60 cm $P = .73$).

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* Corresponding author. Centre for Cardiovascular Genetics, Institute of Cardiovascular Science, University College London, 5 University Street, London, UK WC1E 6JF.

E-mail address: steve.humphries@ucl.ac.uk

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CONCLUSIONS: We show no evidence for statin-related safety or growth issues, but many FH children over the age of 10 years are not on statin treatment. Fewer UK children with FH are obese compared to UK non-FH children.

Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant inherited disorder characterized by elevated low-density lipoprotein cholesterol (LDL-C) levels from birth,[1] with premature coronary heart disease (CHD) occurring in roughly half of men by age 50 years and one-third of women by age 60 years.[2] Statin therapy has been shown to significantly reduce CHD risk in FH patients.[2] Although historically the prevalence of heterozygous FH (HeFH) is thought to be 1 in 500, recent studies have indicated the prevalence of HeFH in the United Kingdom and in countries in Europe may be twice as high.[3–5] The underlying genetic cause for FH is most often due to mutations within the *LDLR* gene, which encodes the low-density lipoprotein receptor, but mutations in apolipoprotein B and proprotein convertase subtilisin/kexin type 9 can produce a phenotype identical to *LDLR* FH.[6] In patients in whom no causative mutation can be found, a polygenic cause of their hyperlipidemia is most likely.[7,8] The detection of the causative mutation in a proband allows cost-effective DNA-based "cascade testing" in the family members, and this approach is recommended in most FH guidelines.[1,9–13] Once identified, the subjects with FH can be offered healthy lifestyle advice (eg, avoiding or stopping smoking) and lipid-lowering therapies.

All recent guidelines for the identification and management of adults and children with FH[1,9–13] have recommended the use of lipid-lowering statin therapy in children. In the United Kingdom, the 2008 NICE guideline (CG71) recommends that statin therapy should be considered by the age of 10 years. In the United Kingdom, atorvastatin is licensed in children over the age of 10 years up to a dose of 20 mg per day, whereas pravastatin is licensed from the age of 8 years with doses of 10–20 mg per day and in older children up to 40 mg daily.[14] Recent European guidelines on the management of FH in childhood proposed that LDL-C be lowered below 3.5 mmol/L if possible.[13] However, the age at which statin use should be started, or its intensity to best prevent the onset of adult premature CHD has not been rigorously established because there are no long-term randomized controlled outcome trials for ethical reasons. Encouragingly, a recent study indicated that initiating statin therapy in childhood resulted in fewer CHD events at a young age than had been seen historically in the parents.[15] There is however considerable short-term randomized and observational data on the utility of statin therapy in children with HeFH, showing a good safety profile, without liver toxicity side effects, no influence on growth trajectory and excellent efficacy in terms of LDL-C reduction over periods of 2–3 years.[16,17] Where it has been examined, there have been no reports of significant increase in muscle pain and/or plasma levels of creatine kinase when on statins.

FH management guidelines, including the UK NICE guideline, recommend that all children (and adults) with HeFH should adopt healthy eating habits, be physically active, and make sensible lifestyle choices, to maintain an ideal body weight.[1,9–13] There is much current concern about the development of obesity in children, with the subsequent influence on morbidity, and a recent study of the Millennium children reported that between 11.8%–14.6% of 5- to 11-year-old UK children are overweight (body mass index [BMI] > 85th percentile) with 11.9%–21.2% being obese (BMI >95th percentile).[18] We are unaware of any comparable data in UK FH children.[18]

The UK National Paediatric Familial Hypercholesterolaemia Register was established in 2012 to collect baseline and long-term follow-up data on all children with HeFH in the United Kingdom. We have previously published baseline data on a subset of these children, which demonstrated that treatment decisions in children with HeFH are appropriately based on a stronger family history of CHD and higher LDL-C.[19] Here, we determined the prevalence of elevated levels of markers of liver toxicity and muscle damage in statin-treated children as an indicator of statin damage and examined the hypothesis that because of the dietary and lifestyle advice they receive, the prevalence of obesity in this cohort of FH children will be lower than that in the general population and that the growth rate from annual follow-up data will be similar in statin-treated and nontreated children.

Methods

All lipid clinics in the United Kingdom and pediatricians with an interest in lipid disorders were contacted electronically and details of the register provided. An electronic web-based data capture tool was developed to collect information. The register captures routine clinical data, demography, family history, treatment, and lifestyle details, and clinicians are sent an electronic reminder to fill in annual follow-up data. Full details of the establishment and governance of the register have been published,[19] as well as the data fields included in the electronic web-based data capture. UK ethical approval was obtained in November 2012 from the NRES Committee North East–Newcastle