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Original Article

Sex differences in cholesterol levels from birth to 19 years of age may lead to increased cholesterol burden in females with FH

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BACKGROUND: The increased risk of cardiovascular disease in familial hypercholesterolemia (FH) is caused by increased cholesterol burden from birth. Even small elevation in cholesterol level accumulates over time and aggravates atherosclerosis.

OBJECTIVES: The aim of the present study was to describe the lipid profile across sex and age in a large cohort of untreated children and adolescents with FH, as this have not clearly been described.

METHODS: FH children (438 girls, 452 boys) not receiving lipid-lowering therapy, aged 0 to 19 years were included and divided into 4 age groups (<5, 5–9, 10–14, and 15–19 years). Information was retrieved from the medical records. Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and non-HDL cholesterol (non–HDL-C) were studied in relation to sex and age by multiple linear regression analysis.

RESULTS: Girls with FH as compared to boys had significantly higher TC, LDL-C, and non–HDL-C ($P < .001$ for all) levels with mean (95% confidence interval) differences of 0.48 mmol/L (0.28, 0.68) (18.6 g/dL), 0.39 mmol/L (0.19, 0.59) (15.08 mg/dL), and 0.42 mmol/L (0.22, 0.63) (16.24 mg/dL), respectively. These estimates did not change after adjustment for age. We also observed sex differences for HDL-C; girls had higher HDL-C in the youngest (<5 years, $P = .05$) and oldest age groups (15–19 years, $P < .001$).

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CONCLUSIONS: FH girls have higher levels of TC, LDL-C, and non–HDL-C levels than boys from birth up to 19 years of age. This may contribute significantly to the total lifelong cholesterol burden in FH women.

Introduction

Familial hypercholesterolemia (FH) is an inherited, autosomal dominant disorder characterized by reduced capacity to clear low-density lipoprotein (LDL) from the circulation.[1] LDL-cholesterol (LDL-C) levels are high from birth in individuals with FH resulting in high lifelong cholesterol exposure and increased risk of premature cardiovascular disease (CVD).[2–4] The atherosclerotic process starts early in life, and higher intima-media thickness of carotid arteries has been reported in children with FH compared to healthy children,[5,6] and intima-media thickness has been reported to be higher in boys than girls with FH.[7,8]

Recently, we showed that mean age of first hospitalization for CVD was 45 years in a cohort of Norwegian patients with FH.[4] Furthermore, mean age of death was 60 years, which is 15 (men) to 21 years (women) earlier than the normal population.[3,9] An interesting finding was that both age at first CVD event and age at death were similar among FH men and women[3,9] in contrast to the general population where there is an almost 10-year gap in age at first CVD event between the sexes.[10] The concept of a total lifelong cholesterol burden defining the risk of disease has developed over the last years.[2] In women, prepregnancy and pregnancy periods without lipid-lowering therapy (LLT) increase the cholesterol burden, as compared to men. However, small differences in cholesterol levels throughout the lifespan, in men and women, could also play a role for CVD risk. The aim of the present study was therefore to study the lipid profile in a large cohort of untreated FH children in relation to sex and age.

Materials and methods

Subjects

Data in this analysis were previously collected retrospectively from medical charts as a cross-sectional review. Children with FH followed at the Lipid Clinic, Oslo University Hospital, Oslo, Norway and the Cardiovascular Genetics Center and the Sophia Children's Hospital of the Erasmus MC Rotterdam, the Netherlands, were included in the study. The study sample has been described previously.[11] In brief, children between the age of 0 and 19 years visiting the Lipid Clinic in Norway between 1990 and September 2010 and children visiting the 2 Dutch lipid clinics between April 1992 and April 2014 were included. Inclusion criteria were that the children should not be on current LLT. Nonetheless, 53 children were excluded from the analysis due to LLT, and therefore, data on untreated lipid values were not available for these children. Seventeen of these were female (mean age 11.8 ± 4.2 years) and 36 were male (mean age 12.2 ± 4.5 years). However, also among this subgroup, the females had significant higher total cholesterol (TC) and LDL-C levels (8.0 mmol/L [309.4 mg/dL] and 6.1 mmol/L [235.9 mg/dL], respectively) compared to the boys (6.9 mmol/L [266.8 mg/dL] and 4.6 mmol/L [177.9 mg/dL], respectively), $P = .045$ and $P = .005$, respectively. In addition, in case of siblings, only 1 sibling was randomly included if the siblings were of same sex; and 1 of each sex was randomly included in case of multiple siblings. All children had a definite FH diagnosis based on genetic testing or clinically based on the Dutch Lipid Clinic Network classification.[2] The Dutch Lipid Clinic Network classification assigns different points for family history of heart disease or hypercholesterolemia, clinical history (eg, family history of premature coronary heart disease [CHD] or cerebral or peripheral vascular disease), tendinous xanthomas or arcus cornea, elevated LDL-C levels and/or an identified mutation in the LDL-R gene, apoB gene, or positive for gain of function PCSK9 mutation. A diagnosis is based upon the total number of points obtained. Definite FH diagnosis requires more than 8 points, probable FH between 6 and 8 points, possible FH between 3 and 5 points, and <3 is classified as unlikely FH if the score is less than 3 points. Demographic characteristics, mutation type, and pretreatment information of weight, height, and levels of blood lipids were collected from the medical records, primarily from the first visit if data were available. Friedewald's equation[12] was used to calculate missing LDL-C values where TC and high-density lipoprotein cholesterol (HDL-C) and triglycerides were available (n = 116). Blood biochemistry parameters including lipids were measured by standard methods at the Oslo University Hospital, Rikshospitalet, Oslo, Norway (NS-EN ISO 15189:2007 accredited) and at the Erasmus MC, Rotterdam, the Netherlands. Children with FH are usually followed up yearly, but it can be shorter or longer depending on individual patient needs or capacity. In a recent register study, we have shown that children with FH seen at the Lipid Clinic in Oslo in the period 2014 to 2016 had a mean age at diagnosis of 8.5 years, age at first visit to the clinic was 9.5 years, and age at initiation of LLT (statins) was 12.5 years. Mean time to next planned visit was 1.4 years.[13] At the Cardiovascular Genetics Center and Sophia Children's hospital in Rotterdam, once statin therapy is initiated, FH children treated initially have a follow-up visit every 3 to 4 months until they are treated to target (LDL-C < 3.5 mmol/L) or are using maximum statin therapy