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Original Article

Treatment goal attainment in children with familial hypercholesterolemia: A cohort study of 302 children in Norway

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BACKGROUND: Consensus statements recommend that statin treatment in children with heterozygous familial hypercholesterolemia (FH) should be considered from 8 to 10 years of age. Although these recommendations are well known, less is known about actual treatment and treatment goal attainment in children with FH.

OBJECTIVE: The objective of the study was to investigate if children with FH were treated according to current recommendations.

METHODS: Retrospective collection of data from medical records of 302 children below 18 years visiting the Lipid Clinic, Oslo University hospital, during 2014 to 2016.

RESULTS: Ninety-nine percent had a genetically verified FH diagnosis. Mean age (standard deviation) at diagnosis, age at first visit, and time followed at the clinic was 8.5 (3.2), 9.5 (2.9), and 4.4 (2.7) years, respectively. Mean pretreatment low-density lipoprotein cholesterol (LDL-C) was 5.4 (1.4) mmol/L. Mean age at start of lipid-lowering therapy (LLT) was 12.5 (2.0) years, with no significant difference between girls and boys. LLT, mainly statins, was used by 177 (59%) children at their last visit. LDL-C in children treated with LLT was 3.6 (1.2) mmol/L (38% reduction from pretreatment, $P < .001$). A treatment goal of LDL-C ≤3.5 mmol/L was achieved by 43% of all children, by 58% of the children on LLT, and by 22% of children not on LLT.

CONCLUSION: Mean age at initiation of LLT is above the recommended 10 years of age and many children did not achieve the LDL-C treatment goal, even with follow-up at a dedicated lipid clinic. Earlier diagnosis and more frequent follow-ups are warranted.

Introduction

Familial hypercholesterolemia (FH) is an inherited, autosomal dominant disorder resulting in reduced capacity to clear low-density lipoprotein (LDL) from the circulation. LDL cholesterol (LDL-C) levels are high from birth resulting in high cholesterol exposure and an increased risk of premature cardiovascular disease (CVD).[1] Recent registry studies from

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Norway have shown that 93% of patients with FH experience CVD during life.[2] CVD mortality was significantly increased in individuals below 70 years, with the highest standardized mortality ratio of 4.12 in the 20- to 39-year age group.[3] Mean age at first hospitalization for CVD was 45 years, with no sex differences, that is, approximately 20 years earlier than in the general population.[4] In children with FH, compared with healthy children without FH, and compared with unaffected siblings, the carotid intima-media thickness (cIMT) has been shown to be significantly thicker before 8 years of age.[5,6] Also, markers of vascular inflammation have been found to be elevated in children with FH.[6]

The introduction of statins (hydroxy-methylglutaryl-coenzyme A reductase inhibitors) around 1990 revolutionized the treatment of FH. Compared with the prestatin era, the risk of CVD has been substantially reduced. However, a considerable residual risk remains, especially when treatment starts late in life,[4,7] and possibly also when treatment and follow-up is done outside specialized clinics.[8,9] Pravastatin treatment from 8 years of age in children with FH was associated with normalization of cIMT progression after 10-year follow-up, with no serious events reported.[10] Also, a younger age at the start of statin treatment was associated with lower cIMT after 10 years. Importantly, no one in this cohort had CVD before 30 years of age, unlike their parents in whom 7% experienced CVD before 30 years of age.[11] Recently, rosuvastatin treatment over 2 years in children with FH, aged 6 to 17 years, resulted in slowing cIMT progression, compared with untreated, unaffected siblings, and the significant difference in cIMT between the 2 groups at baseline was no longer significant by year 2 of the study.[12] The findings in these studies support the assumption that early initiation of statin therapy may be beneficial in children with FH.

Consensus statements from the European Atherosclerosis Society (EAS) recommend that statin treatment in children with FH should be considered from 10 years of age or from 8 years of age in high-risk individuals.[1,13] A treatment goal of LDL-C <3.5 mmol/L was recommended. Although these recommendations are well known, less is known about actual treatment, goal attainment, tolerance, and adherence in children and adolescents with FH.

The aim of the present study was to investigate if children with FH, seen at the Lipid Clinic, Oslo University Hospital, were treated according to current recommendations.

Material and methods

Subjects and data collection

Data were collected retrospectively to a treatment quality register, from medical records of children below 18 years with a diagnosis of heterozygous FH, visiting the Lipid Clinic, Oslo University hospital, during 2014 to 2016. Only children with a confirmed pathogenic mutation in the *LDL-receptor* gene, the *proprotein convertase subtilisin/kexin type 9* gene, or the R3500Q mutation in the *apolipoprotein B* gene, or children with elevated LDL-C levels and a first- or second-degree relative with such a mutation, were included. Children with homozygous or compound heterozygous FH were excluded. To obtain treatment data, only children with at least one prior visit to the clinic were included in the register. Children were divided into 2 groups, designated as lipid-lowering therapy (LLT) and no LLT, according to whether they received LLT or not, at the last visit. All genetic tests were performed by the Unit for Cardiac and Cardiovascular Genetics at Oslo University Hospital. Data on diagnosis, lipid levels, other relevant blood chemistry, LLT, diet, and smoking habits were collected. Standard procedure in our clinic is to take blood samples locally and send them to the Department of Medical Biochemistry, Oslo University Hospital, for analysis, using their standard methods. From 2001, this laboratory has measured LDL-C by the direct enzymatic method. A small number of blood samples might have been analyzed by independent or local hospital laboratories. Dietary data were collected by SmartDiet, a short self-instructing questionnaire on diet and lifestyle. The questionnaire was developed by the Lipid Clinic, Oslo University Hospital, to easily assess diet and lifestyle habits in clinical settings and was validated in 2002 among adults.[14] The questionnaire is completed by the child and parent before the consultation and reviewed at the consultation. The maximum score is 41 points. A low score ($\leq$27 points) indicates a non-heart-healthy diet, a middle score (28–35 points) indicates a diet with room for improvement, and a high score ($\geq$36 points) indicates a heart-healthy diet. The treatment quality register was approved by the Regional Committee for Medical and Health Research Ethics and the Data Protection Official at Oslo University Hospital. Informed consent is not required in Norway for this type of data collection used for quality of treatment purposes.

Statistical methods

Results are presented as means and standard deviations for continuous variables when normally distributed and as medians and ranges when non-normally distributed. Categorical variables are presented as frequencies and percentages. Comparisons between 2 groups were performed using Student's *t*-test or Mann-Whitney *U* test for continuous variables, depending on the distribution and the chi-square test or Fisher's exact test for categorical variables depending on the expected cell frequencies. Statistical analyses were conducted in SPSS (version 21). All tests were 2 sided. A 5% level of significance was used.

Results

Demographic data and pretreatment lipid levels

Among the 314 children in the treatment quality registry, 302 children were included in the data analysis, according to our inclusion and exclusion criteria. There were an equal