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Cascade screening and treatment of children with familial hypercholesterolemia in Turkey

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Abstract

Objectives: Premature coronary artery disease is the most common preventable cause of death in developed countries, and familial hypercholesterolemia (FH) is the most common monogenetic disorder of lipid metabolism, predisposing for premature coronary artery. FH is the most common preventable cause of death in developed countries. In 2016, the national lipid screening program in school-age children has been started in Turkey. In this study, we aimed to evaluate the efficacy of lipid screening program, lipid-lowering treatments, and the challenges of treatments in children diagnosed with FH.

Methods: Patients diagnosed with FH in the pediatric metabolism outpatient clinic were retrospectively evaluated. Changes in lipid profile with dietary interventions and statin treatments were assessed. The results of cascade screening were analyzed.

Results: Fifty-one patients diagnosed with FH were enrolled in the study. Twenty-four (47.1%) were female. The mean age of the patients was 9.8 ± 3.2 years. Heterozygous *LDLR* gene mutation was detected in all patients. Three novel pathogenic variations were revealed with the genetic investigation. Forty-one (80.4%) patients had high adherence to CHILD-2 dietary recommendations. The mean low-density lipoprotein cholesterol (LDL-C) level decreased by 14.5 ± 7.6% after dietary intervention. Parents refused to start statin treatment in 8 (15.7%) patients. Statin treatment was initiated to 22 (43.1%) patients. Mean LDL-C level decreased from 204.1 ± 19.1 mg/dL to 137.0 ± 13.1 mg/dL. In cascade screening, 7 (13.7%) parents without a diagnosis of FH were diagnosed with FH. After the screening program, statin treatment was initiated for 18 (35.3%) parents and 7 (16.3%) siblings.

Conclusions: We can conclude that screening for FH in children is crucial for diagnosing FH not only in children but also in their relatives. Although statins are safe and effective in achieving the target LDL-C level, we determined significant resistance for initiating statin treatment in patients.

Keywords: children; familial hypercholesterolemia; low-fat diet; statin.

Introduction

Familial hypercholesterolemia (FH) is the most common disorder of lipid metabolism, and it manifests with very high levels of low-density lipoprotein cholesterol (LDL-C). High levels of LDL-C are associated with premature coronary artery disease, which is the most common preventable cause of death in developed countries [1]. Therefore, early diagnosis and appropriate treatment have a crucial role in preventing premature coronary artery disease. However, most children with FH remain undiagnosed. At this point, the screening of lipid disorders in children has been discussed. While some authors recommended the cascade screening (screening the children with a family history of early atherosclerotic disease or high cholesterol level), some studies suggested the universal screening in pediatric age group [2–5]. Oppositely, US Preventive Services Task Force concluded that there is insufficient evidence for the screening of dyslipidemia in those aged less than 20 years [6]. In 2016, the national lipid screening program in school-age children has been started in Turkey [7]. The screening program includes all children between 5 and 18 years of age. Family physicians examine the risk factors (family history and obesity, diabetes mellitus, hypertension, smoking) and lipid profile of children. Children with LDL-C ≥190 mg/dL (4.9 mmol/L) or LDL-C ≥160 mg/dL

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(4.1 mmol/L) with risk factors are referred to metabolism departments to be evaluated for the diagnosis of FH. In addition, children with LDL-C ≥130 mg/dL (3.4 mmol/L) with FH-diagnosed parents are assessed for FH.

Early low-fat dietary interventions and statin treatment in FH is important for better clinical outcomes [8, 9, 10]. However, the fear of adverse effects causes strong parents' concern about the initiation of statin treatment for their children [11, 12].

In this study, we aimed to evaluate the efficacy of dietary interventions and statin treatment and the challenges of treatments in children diagnosed with FH by the lipid screening program. This study's secondary aim was to determine the efficacy of the screening program on FH diagnosis.

Materials and methods

Patients diagnosed with FH in the pediatric metabolism outpatient clinic between September 2018 and December 2019 were retrospectively evaluated. All patients were referred by family physicians with suspected hypercholesterolemia during the lipid screening program at schools. The patients in whom the FH diagnosis was based on mutation analysis in *LDLR*, *APOB*, *LDLRAP1*, and *PCSK9* gene were enrolled in the study.

Demographic and clinical findings (age, gender, family history of dyslipidemia, lipid-lowering treatment or premature symptomatic coronary artery disease, body mass index [BMI]) were recorded. For all patients, the CHILD-2 diet, which includes restriction of saturated fat intake to less than 7% of daily calories and a decrease in daily cholesterol intake to 200 mg or less, was initiated [13]. Dietary adherence was assessed with parents' statement and diet list of the last three days. Cholesterol intake above 200 mg/day and high intake of saturated fat above recommended amount for at least one day are defined as low adherence. Under a low-fat diet, the lipid profile of all patients was recorded. Patients were evaluated for the initiation of statin treatment. Statin treatment is initiated at the lowest recommended dose. According to the European Atherosclerosis Society Consensus Panel, the dose is up-titrated in accordance with the LDL-C–lowering response and tolerability [14]. From 10 years of age, the target LDL-C level is 130 mg/dL (3.5 mmol/L), and for children between 8 and 10 years of age, 50% reduction from pretreatment levels is aimed. In patients aged less than 8 years or refused medical treatment, statin treatment was not initiated. Under statin treatment, control lipid profile and adverse reactions were noted.

The lipid profile of the parents and siblings of patients were investigated. One patient was excluded from the study because of irregular clinical follow-up. Informed consent was obtained from the parents of the children before participation in the study.

Statistical analysis

Categorical variables (gender, family history of hyperlipidemia, lipid-lowering treatment, and premature coronary artery disease, genetic mutations in the *LDLR* gene) were expressed as numbers and percentages, and continuous variables (age, follow-up period, total cholesterol (TC), LDL-C, triglyceride and high-density lipoprotein cholesterol (HDL-C) levels, and changes in lipid profile) were expressed as mean ± standard deviation (minimum-maximum). The normality of data was assessed with Kolmogorov-Smirnov and Shapiro-Wilk tests. The relation between dietary adherence and age of the patients was analyzed with independent samples t-test. The effect of a low-fat diet and statin treatment on the lipid profile of patients was assessed with paired-samples t-test or Wilcoxon test. A chi-square test was used to evaluate the relationship between dietary adherence and gender of patients.

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) computer software (version 21.0; SPSS, Chicago, IL). A two-tailed p-value <0.05 was considered statistically significant.

Results

Fifty-one patients diagnosed with FH were enrolled in the study. Twenty-four (47.1%) were female, and 27 (52.9%) were male. The mean age of patients was 9.8 ± 3.2 (5–17) years. Assessed from family history, FH in parents was declared by 44 (86.3%) patients, and 17 (33.3%) parents were receiving lipid-lowering treatment. Coronary artery disease was detected in 3 (2.9%) parents. At physical examination, BMI standard deviation score of all patients was below two.

In patients' diagnosis of FH, the mean TC, LDL-C, HDL-C, and triglyceride levels of patients were 313.1 ± 46.0 mg/dL (236–419), 237.4 ± 45.2 mg/dL (163–337), 58.5 ± 14.1 mg/dL (30–89), and 79.8 ± 20.8 mg/dL (49–123), respectively. Heterozygous *LDLR* gene mutations were detected in all patients. Twenty-six different mutations and three novel pathogenic variations (p.C46W (c.138C>G), p.D277N (c.679G>A), p.I560F (c.1678A>T)) were revealed with the genetic investigation. The most frequent mutation in the *LDLR* gene was p.W577R (c.1729T>C) (Table 1).

CHILD-2 diet was initiated for all patients. The mean follow-up period with the dietary treatment was 100 days (91–132). Forty-one (80.4%) patients had high adherence to dietary treatment. No relation was detected between age, the gender of patients, and dietary adherence (p=0.675, p=0.870). Mean LDL-C level decreased from 237.3 ± 44.9 mg/dL (163–337) to 200.9 ± 30.9 mg/dL (146–278), and this change was statistically significant (p<0.0001). Mean LDL-C level decreased by 14.5 ± 7.6% (–7.1–36.0) (p<0.0001). Although a significant decrease was observed in the triglyceride level, there was no difference in HDL-C level with a low-fat diet (Table 2).

Eighteen (35.3%) patients aged less than eight years were not eligible for statin treatment. Parents refused to start statin treatment in 8 (15.7%) children. The mean age of

Table 1: The list of mutations in *LDL*R gene.

No.	Mutations	n	%
1	p.W577R (c.1729T>C)	7	13.7
2	p.G549D (c.1646G>A)	4	7.8
3	p.S286R (c.858C>A)	4	7.8
4	p.Y188X (c.564C>G)	3	5.9
5	p.A540T (c.1618G>A)	2	3.9
6	p.C197X (c.591C>A)	2	3.9
7	p.D139N (c.415G>A)	2	3.9
8	p.E408K (c.1222G>A)	2	3.9
9	p.I488T (c.1463T>C)	2	3.9
10[a]	p.I560F (c.1678A>T)	2	3.9
11	p.Q739X (c.2215C>T)	2	3.9
12	p.R350X (c.1048C>T)	2	3.9
13	IVS15-3C>A (c.2311+1G>A)	1	2.0
14	IVS4-1G>A (c.695-1G>A)	1	2.0
15	IVS5-1G>A (c.818-1G>A)	1	2.0
16	p.A431T (c.1291G>A)	1	2.0
17	p.C222R (c.664T>C)	1	2.0
18	p.C27W (c.81C>G)	1	2.0
19[a]	p.C46W (c.138C>G)	1	2.0
20	p.C95W (c.285C>G)	1	2.0
21[a]	p.D277N (c.679G>A)	1	2.0
22	p.E228K (c.682G>A)	1	2.0
23	p.F114Lfs[a]13 (c.340_344delTTTCG)	1	2.0
24	p.F282L (c.846C>A)	1	2.0
25	p.E228Q (c.682G>C)	1	2.0
26	p.K609X (c.1807A>T)	1	2.0
27	p.P699L (c.2096C>T)	1	2.0
28	p.S493CfsX42 (c.1478_1479delCT)	1	2.0
29	p.Y456C (c.1394A>G)	1	2.0

[a] Novel pathogenic variants.

these children was 11.6 ± 2.2 (8–16) years. Among them, three children were between 8 and 10 years of age. In 4 (7.8%) patients, statin treatment was discontinued because of the inability of children to swallow statin tablets. These patients were 8, 9, 9, and 11 years old, respectively, and statin treatment was initiated in 22 (43.1%) patients. The mean follow-up period with the statin treatment was 221 days (34–310). While 18 patients were treated with atorvastatin, pravastatin was initiated in four patients. Mean LDL-C level decreased from 204.1 ± 19.1 mg/dL (154–256) to 137.0 ± 13.1 mg/dL (102–156) ($p<0.0001$). Changes in triglyceride and HDL values were not significant (Table 3). In the clinical follow-up, no adverse reaction was observed.

In cascade screening, 7 (13.7%) parents without diagnosis of FH were diagnosed with FH. Among these, 3 (5.9%) parents refused statin treatment. Fourteen (27.5%) of 27 parents who had already diagnosed with FH were followed up without statin treatment. Overall, after the screening program, statin treatment was initiated for 18 (35.3%) parents (Figure 1). Fourteen (32.6%) of 43 siblings were diagnosed with FH, and seven (16.3%) siblings were treated with statins (Figure 2).

Discussion

It is previously mentioned that, when looking at the siblings and parents of children diagnosed with FH, almost half of the siblings and at least one of the parents have LDL-C and TC elevation [9]. In accordance with the Spanish study, cascade screening in 87 children with FH revealed the diagnosis of FH in 41 parents [15]. Consistently, in our study, 13% of parents and 32% of siblings were newly diagnosed with FH by cascade screening. The lipid screening program plays a significant role not only in children but also in their relatives in the diagnosis of FH. We believe that this is the most important finding in this study, in which the lipid screening program was evaluated. Early diagnosis and treatment of FH prevent patients from CAD and its complications [1].

The first-step treatment in FH is lifestyle changes such as fat-modified diet, exercises, and smoking cessation [14, 16]. Generally, the CHILD-2 diet, which limits the saturated fat intake to 7% of total daily calories and recommends cholesterol intake less than 200 mg/day, is recommended for children [13, 16]. However, lifestyle changes are insufficient to reduce LDL-C to the target level [8]. We found high adherence (80%) to low-fat diet, and a 14.5% decrease in LDL-C level was observed after dietary treatment. As expected, none of the patients with high adherence to diet reached the target LDL-C levels.

In the recent consensus, recommended target LDL-C levels for children older than 10 years are <160 mg/dL (<4 mmol/L) [17, 18]. Treatment goals for children aged 8–10 years in guidelines varies, some says <160 mg/dL (<4 mmol/L), some <130 (<3.5 mmol/L), and others 50% reduction. The 8- to 10-year-old children selected for initiation of statin treatment are usually high-risk children, that is, not all children with FH aged 8–10 years should initiate statin treatment [14, 17, 18]. Lipid-lowering medical therapy is usually necessary to achieve targeted LDL-C levels. Generally, statins are the first-line medical treatment of FH. While pravastatin is approved for patients older than eight years, other statins such as atorvastatin, simvastatin, lovastatin, and rosuvastatin can be used for patients older than10 years [19]. Studies have shown that LDL-C levels reduced between 23% and 34% under pravastatin treatment in FH-diagnosed children [20, 21]. McCrindle et al. reported that a 40% reduction in LDL-C level was observed with atorvastatin treatment [22].

Table 2: Changes in lipid profile of patients with high and low adherence to diet.

Lipid profile	High adherence to diet (n=41)				Low adherence to diet (n=10)			
	Before dietary treatment	After dietary treatment	p-Value	Change (%)	Before dietary treatment	After dietary treatment	Change (%)	p-Value
TC mean ± SD (min-max), mg/dL	311.4 ± 44.9 (244–419)	273.8 ± 32.9 (201–386)	<0.0001	11.5 ± 7.8 (−6.7–33.0)	320.1 ± 52.4 (236–379)	319.6 ± 51.4 (232–409)	−0.08 ± 6.2 (−9.4–9.0)	0.838
LDL-C mean ± SD (min-max), mg/dL	237.3 ± 44.9 (163–337)	200.9 ± 30.9 (146–278)	<0.0001	14.5 ± 7.6 (−7.1–36.0)	237.8 ± 49.4 (169–305)	247.6 ± 53.9 (170–317)	−5.5 ± 20.9 (−35.9–18.4)	0.139
HDL-C mean ± SD (min-max), mg/dL	58.1 ± 14.0 (30–87)	58.1 ± 12.7 (36–86)	0.334	−1.5 ± 12.8 (−23.5–27.3)	60.4 ± 15.2 (46–89)	61.2 ± 11.9 (48–78)	−3.2 ± 15.0 (−34.6–19.1)	0.837
Triglyceride mean ± SD (min-max), mg/dL	81.1 ± 21.3 (49–123)	67.3 ± 19.5 (39–146)	<0.0001	13.8 ± 24.3 (−46.1–60.2)	74.4 ± 18.3 (49–109)	77.4 ± 20.3 (56–106)	−4.1 ± 7.5 (−17.1–7.7)	0.721

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; min, minimum; max, maximum; SD, standard deviation; TC, total cholesterol.

Table 3: Changes in lipid profile of patients with statin treatment (n=22).

Lipid profile	Before statin treatment	After statin treatment	p-Value	Change (%)
TC mean ± SD (min-max), mg/dL	281.1 ± 19.2 (248–333)	207.5 ± 25.2 (178–291)	<0.0001	26.1 ± 9.1 (−7.8–24.9)
LDL-C mean ± SD (min-max), mg/dL	204.1 ± 19.1 (154–256)	137.0 ± 13.1 (102–156)	<0.0001	32.7 ± 5.0 (24.1–42.0)
HDL-C mean ± SD (min-max), mg/dL	61.9 ± 11.8 (42–86)	59.5 ± 10.0 (42–82)	0.745	1.9 ± 16.6 (−33.3–41.6)
Triglyceride mean ± SD (min-max), mg/dL	71.5 ± 24.9 (39–146)	62.9 ± 19.0 (29–108)	0.134	6.4 ± 31.3 (−64.4–57.6)

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; min, minimum; max, maximum; SD, standard deviation; TC, total cholesterol.

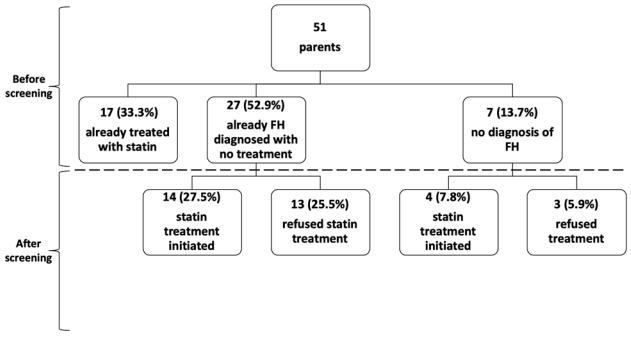

Figure 1: The diagnosis and treatment status of parents after cascade screening.

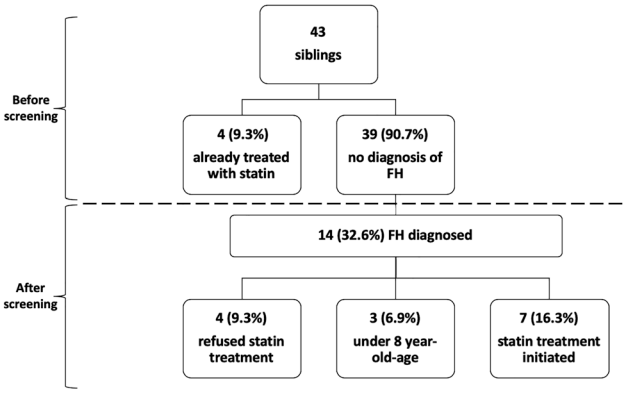

Figure 2: The diagnosis and treatment status of siblings after cascade screening.

Consistent with the literature, we determined a 32% reduction in LDL-C level with statin treatment. In all patients treated with statins, the targeted LDL-C level was reached.

Another striking finding of our study is parents have a strong concern about the initiation of statin treatment. Kinnear et al. documented that the concern about long-term safety and potential side effects of FH medication are substantial barriers to treatment adherence in FH [11]. Concerns about the side effects of statins are the main reason for refusing to take medication [12]. However, long-term studies showed that severe side effects of statins are

rare [10, 23]. A recent prospective cohort study with 20 years follow-up has found no serious adverse reaction and no significant change in liver function tests and creatine kinase levels in children with FH under statin treatment [10]. In our study, parents refused to start statin treatment in 15.7% of children. Three of eight children were aged between 8 and 10 years.

Furthermore, almost 14% of parents and 10% of siblings diagnosed with FH decided not to initiate statin treatment. All these findings suggest that parents in our country need to be convinced that statins are safe and necessary for the treatment of FH to prevent premature coronary artery disease. Although all children treated with statins had high compliance of statin treatment with no side effects, four children could not continue treatment because of the inability to swallow the tablets. Seventy-five percent of children were aged less than 10 years. This situation also shows the necessity of chewable or crushable tablets of statins for children.

Although it is expensive and cannot be performed in all centers, FH diagnosis in children should be established with genetic analysis, which is considered as the gold standard [24]. In the genetic analysis we performed, heterozygous *LDLR* gene mutation was detected in all patients. In a Turkish study, the most common *LDLR* gene mutation in FH-diagnosed patients was p.W577R (c.1729T>C) [25]. Consistently, p.W577R (c.1729T>C) mutation in the *LDL*R gene was the most common mutation in our study. Although we did not observe genotype-phenotype relation, three novel variations (p.C46W (c.138C>G), p.D277N (c.679G>A), p.I560F (c.1678A>T)) were revealed with this study. We believe that further mutation reports may be helpful in evaluating the genotype-phenotype relationship.

There are several limitations of this study. First, the follow-up period in patients undergoing dietary changes and statin therapy was not sufficient to evaluate the clinical outcomes and long-term effects and side effects of the treatment. Second, no information about the physical activity of patients was noted. Therefore, we did not evaluate the relationship between physical activity and lipid profile. Third, the low number of patients in the subgroups limited us to better analyze cascade screening results, treatment outcomes, and treatment side effects.

As a result, we can conclude that screening FH in children is crucial for diagnosing FH not only in children but also in their relatives. Although statins are safe and effective in achieving the target LDL-C level, we determined a significant resistance for initiating statin treatment in patients. Long-term, multicenter prospective studies are necessary to better understand the effectiveness of the screening program and the efficacy and side effects of dietary and statin treatments.

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