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Clinical and Laboratory Evaluation of Cases with Familial Hypercholesterolemia: A Multicentre Study

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Abstract

Aim: Familial hypercholesterolemia leads to the buildup of atherosclerotic plaques in the arteries, greatly elevating the risk of early-onset coronary heart disease. The objective of this study was to examine the clinical, laboratory, and genetic profiles of patients affected by familial hypercholesterolemia.

Methods: A retrospective review was performed on the demographic, clinical, biochemical and genotypic profiles of 124 individuals diagnosed with familial hypercholesterolemia.

Results: These cases from 6 centres comprised 50.8% males and 49.2% females. There was a history of hypercholesterolemia in the mothers of 43.5% of the cases and in the fathers of 53.2%. At the time of diagnosis, 81.5% of the cases had no complaints, 3.2% had skin lesions and 3.2% had weight gain complaints. Mutations were detected in the LDLR gene in 95.2% of the cases, in the APOE gene in 3.2% and in the APOB gene in 1.6%.

Conclusion: Familial hypercholesterolemia cases are still under-detected both in Türkiye and worldwide. Consequently, the prevention of coronary artery diseases caused by hypercholesterolemia is not feasible, underscoring the need for implementing more robust and widespread screening protocols.

Keywords: Familial hypercholesterolemia; LDL-cholesterol; Atherosclerosis; Lipoprotein apheresis

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Ailevi Hiperkolesterolemili Vakaların Klinik ve Laboratuvar özelliklerinin Değerlendirilmesi: çok Merkezli Çalışma

Öz

Amaç: Ailevi hiperkolesterolemi, arteryel damarlarda aterosklerotik plak birikimine neden olur ve genç yaşta koroner kalp hastalığı riskini önemli ölçüde artırır. Bu çalışmanın amacı, ailevi hiperkolesterolemili hastaların klinik, laboratuvar ve genetik özelliklerini değerlendirmektir.

Yöntemler: Ailevi hiperkolesterolemili 124 hastanın demografik, klinik, biyokimyasal ve genotipik özellikleri retrospektif olarak incelendi.

Bulgular: Bu 6 merkezden toplanan olguların %50,8'i erkek ve %49,2'si kızlardan oluşmaktaydı. Vakaların %43,5'inin annesinde ve %53,2'sinin babasında hiperkolesterolemi öyküsü vardı. Tanı anında vakaların %81,5'inin hiçbir şikayeti yok iken, %3,2'sinde cilt lezyonları ve %3,2'sinde kilo alma şikayeti vardı. Mutasyonlar vakaların %95,2'sinde LDLR geninde, %3,2'sinde APOE geninde ve %1,6'sında APOB geninde tespit edildi.

Sonuç: Ailevi hiperkolesterolemi vakaları hem Türkiye'de hem de dünya çapında hala yeterince saptanamamaktadır. Sonuç olarak, hiperkolesterolemiye bağlı koroner arter hastalıkları önlenememektedir, bu nedenle daha etkili ve kapsamlı tarama prosedürlerine açık bir ihtiyaç vardır.

Anahtar kelimeler: Ailevi hiperkolesterolemi, LDL-kolesterol, Ateroskleroz, Lipoproteinaferezi.

INTRODUCTION

Familial hypercholesterolemia (FH) is a genetic disorder passed down in an autosomal dominant manner, causing elevated concentrations of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C)[1–3]. Due to the accumulation of atherosclerotic plaque in the arteries caused by FH, the likelihood of early-onset coronary heart disease (CHD) is greatly increased[2,4].

Homozygous familial hypercholesterolemia is a rare and life-threatening disease initially clinically characterized by plasma cholesterol levels >13 mmol/L (>500 mg/dL), diffuse xanthomas, and marked early and progressive atherosclerotic cardiovascular disease[5,6].

The prevalence of heterozygous FH in the general population is estimated to be one in 200 to 300 people. Homozygous familial hypercholesterolemia, on the other hand, is relatively rare, with an estimated prevalence of 1:300,000 to 1:400,000[5,7,8].

Patients with FH have predominantly excess coronary heart disease rather than cerebral or peripheral artery disease. The risk of early coronary heart disease increases approximately 20-fold in heterozygous FH, with the highest risk occurring in untreated young males[9]. Patients diagnosed with homozygous FH may usually experience the first cardiovascular event in adolescence, nonetheless, early manifestations, including angina pectoris, have been documented in childhood[10,11].

The objective of this study was to assess the clinical, laboratory, and genetic features of familial hypercholesterolemia patients who were seen at six centres until August 2023. Thus, this study is expected to fill a significant gap in the literature by providing original and detailed data that can support clinicians in the diagnosis and management of familial hypercholesterolemia in childhood.

METHOD

Patients and laboratory analyses

A retrospective evaluation was made of the clinical characteristics in the patient files of 124 paediatric cases diagnosed with familial hypercholesterolemia in 6 Paediatric Metabolism Clinics in Türkiye. The patients comprised63 (50.8%) males and 61 (49.2%) females. The diagnosis of familial hypercholesterolemia was defined as the

presence of a pathogenic genetic mutation related to the clinical condition or LDL cholesterol level>130mg/dl showing the familial characteristic.

Data were recorded retrospectively from the patient files of gender, age at diagnosis, current age, bodyweight at the time of diagnosis, weight to height ratio at the time of diagnosis, parental history of hypercholesterolemia, parental history of myocardial infarctus, parental consanguinity, complaints on presentation, physical examination findings, the presence of hepatosteatosis on ultrasonography (USG), carotid intima media thickness measured on USG, diagnostic pathway, glucose, AST, ALT, total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels at the time of diagnosis, treatments received, treatment response rates, genetic analysis results, liver transplantation information, and data of LDL apheresis.

Subjects under the age of 18 with an LDL cholesterol level exceeding 130 mg/dL, or harboring a pathogenic genetic variant associated with elevated LDL cholesterol levels, were included in the study. Individuals aged over 18 years at the time of diagnosis, those with LDL cholesterol levels below 130 mg/dL, or those with medical conditions known to cause secondary hypercholesterolemia were excluded from the study.

As this was a retrospective study, no prior sample size calculation was performed. All eligible cases meeting the inclusion criteria within the defined time period were included in the analysis.

Genetic analyses were performed either as single-gene sequencing or as part of a multi-gene panel, depending on the clinical context and the availability of diagnostic tools at each center. In cases where clinical suspicion strongly pointed toward familial hypercholesterolemia, sequencing of the LDLR gene was prioritized. For broader diagnostic assessment, a multi-gene panel including LDLR, APOB, PCSK9, APOE, and other lipid metabolism-related genes was employed. Ethical clearance for the research was granted by the Local Ethics Committee (Protocol no: 2024/08-48, dated: 23 May 2024). This study was managed accordingly with the Declaration of Helsinki. Because the study had a retrospective design, no informed consent was required from the legal guardians of the cases.

Statistical Analyses

Statistical analysis of the study data was performed using SPSS version 22 software (SPSS Inc., Chicago, IL, USA). Continuous variables were summarized with mean ± standard deviation (SD), median, minimum, and maximum values, while categorical variables were expressed as counts (n) and percentages (%). To evaluate potential differences in total cholesterol and LDL cholesterol levels at diagnosis between heterozygous and homozygous familial hypercholesterolemia cases, the Mann-Whitney U test was performed, with statistical significance set at $p<0.05$.

RESULTS

Demographic findings

The average age of patients at diagnosis was 8.2±4.51 years (range: 0.6–17 years), while at the time of data collection, it was 11.7±5.02 years (range: 1–24 years). At the time of diagnosis the mean age of cases was 7.9±5.13 years for those diagnosed with selective family screening, 8.3±3.94 years for those diagnosed with universal screening, and 8.6±4.90 years for those diagnosed incidentally. Due to the non-normal distribution of the data, a chi-square test was conducted to examine significant differences between them. No significant difference was determined in the ranges ($p=0.877$, $p=0.087$, and $p=0.934$, respectively).

At the time of diagnosis, the mean weight according to height ratio was 104±20.1% (range, 61-161%). Accordingly, 12% of the cases were evaluated as overweight, and 17.7% as obese. Parental consanguinity was present in 33.9% of the cases. A history of hypercholesterolemia was present in the mothers of 43.5% of the cases and in the father of 53.2%. A history of myocardial infarctus experienced at a young age was present in the mother in 1.6% of the cases and in the father in 15.3%. The diagnosis was made incidentally in 21 (16.9%) cases during investigation of an unrelated complaint, from selective family screening in 42 (33.9%) cases, and from universal screening in 61 (49.2%).The general characteristics of the cases are shown in Supplementary material 1.

Supplementary Material 1: Demographic, clinical, laboratory and genetic analysis findings of the cases included in the study

Case no	Gender	Age of diagnosis (year)	Maternalhypercholesterolemia	Maternal MI history	Paternalhypercholesterolemia	Paternal MI history	Total cholesterol (mg/dl)	LDL cholesterol (mg/dl)	Treatment	Gene	variant
1	M	9.0	No	-	Yes	-	231,00	151.0	Diet	LDLR	c.1060+10G>C heterozygote
2	M	3.0	Yes	-	Yes	-	232,00	153.3	No	APOB	c.7890G>C heterozygote
3	F	12.0	No	-	Yes	-	221,00	165.7	Diet+statin	LDLR	c.1678A>T heterozygote
4	M	10.0	Yes	-	Yes	-	229,00	169.0	Diet	LDLR	c.1502C>T heterozygote
5	M	0.6	No	-	No	-	243,00	181.7	Diet	Undetected	
6	F	1.5	Yes	-	Yes	-	216,00	186.0	No	LDLR	c.1729T>C heterozygote
7	M	17.0	Yes	-	Yes	+	246,00	190.2	Diet	NA	
8	M	7.0	No	-	Yes	-	260,00	197.3	Diet	LDLR	c.1678A>T heterozygote
9	F	3.0	No	-	No	-	257,00	199.2	Diet	NA	
10	F	11.0	Yes	+	No	-	260,00	215.5	Diet+statin	Undetected	
11	F	9.0	Yes	-	No	-	279,00	215.5	Diet+statin	LDLR	c.664T>C heterozygote
12	M	9.0	No	-	Yes	+	281,00	237.9	Diet+statin	LDLR	c.1678A>T heterozygote
13	F	7.0	No	-	Yes	-	310,00	255.2	Diet	Undetected	
14	M	3.5	Yes	-	No	-	334,00	259.0	Diet	LDLR	c.1730G>C heterozygote
15	F	16.0	No	-	Yes	+	330,00	263.4	Diet+statin	LDLR	c.1260_1266del heterozygote
16	F	6.0	Yes	+	No	-	303,00	274.2	Diet+statin	Undetected	

17	M	17.0	Yes	-	Yes	-	336,00	282.6	Diet	NA	
18	M	1.0	Yes	-	Yes	-	342,00	294.0	Diet	LDLR	c.1729T>C heterozygote
19	F	16.0	No	-	Yes	-	375,00	301.2	Diet+statin	APOE	c.500-502DelTCC heterozygote
20	M	11.0	No	-	Yes	+	370,00	320.6	Diet+statin	NA	
21	M	5.0	Yes	-	Yes	-	704,00	691.0	Diet+statin+ezetimibe+apheresis	LDLR	c.1729T>C homozygote
22	F	2.0	Yes	-	Yes	-	710,00	710.0	Diet+statin+ezetimibe+apheresis	LDLR	c.1729T>C homozygote
23	F	1.0	Yes	-	Yes	-	810,00	750.0	Statin	LDLR	c.1729T>C homozygote
24	M	3.0	Yes	-	Yes	-	1016,00	929.5	Diet+statin	LDLR	c.1729T>C homozygote
25	F	0.6	Yes	-	No	-	195,00	134.0	No	LDLR	c.1514G>A heterozygote
26	M	10.0	No	-	Yes	-	303,00	207.6	Statin	LDLR	c.378delC heterozygote
27	F	12.0	No	-	No	-	273,00	218.0	Diet+statin	LDLR	c.2389G>A heterozygote
28	F	6.0	Yes	-	No	-	342,00	237.3	Diet	LDLR	c.1514G>A heterozygote
29	M	11.0	No	-	No	-	317,00	253.2	Statin	LDLR	c.2389G>A heterozygote
30	F	2.0	No	-	No	-	366,00	263.6	Diet+statin	LDLR	c.1729T>C heterozygote
31	M	5.0	No	-	No	-	364,00	264.0	Diet	LDLR	c.378delC heterozygote
32	F	10.0	Yes	-	No	-	350,00	293.0	Diet+statin	LDLR	c.2389G>A heterozygote
33	F	3.0	No	-	No	-	881,00	747.6	Statin	LDLR	c.1729T>C heterozygote
34	M	9.0	Yes	-	Yes	-	239,00	141,00	Diet+statin	Undetected	
35	M	7.0	No	-	No	-	222,00	153,00	Diet+omega 3	Undetected	
36	M	5.0	Yes	-	Yes	-	226,00	154,00	Diet+omega 3	NA	
37	M	4.0	No	-	Yes	-	235,00	158,00	Diet	Undetected	
38	F	4.0	Yes	-	No	-	234,00	160,00	Diet	NA	
39	M	10.0	No	-	No	-	249,00	166,00	Diet	APOE	c.388T>C heterozygote
40	F	9.0	No	-	No	-	217,00	172,00	Diet+omega 3+statin	Undetected	
41	F	8.0	Yes	-	Yes	-	250,00	173,00	Diet+omega 3	LDLR	

42	M	5.0	Yes	-	No	-	254,00	176,00	Diet+omega 3	LDLR	c.1567G>A heterozygote
43	F	14.0	Yes	-	Yes	+	267,00	181,00	Diet+statin	NA	
44	M	7.0	Yes	-	No	-	259,00	182,00	Diet	NA	
45	F	12.0	No	-	No	-	230,00	185,00	Diet+omega 3	NA	
46	M	13.0	Yes	-	No	-	265,00	188,00	Diet	LDLR	c.858C>A heterozygote
47	M	10.0	No	-	No	-	266,00	189,00	Diet	Undetected	
48	M	5.0	No	-	Yes	-	252,00	193,00	Diet+statin	LDLR	c.1502C>T heterozygote, c.1060+7T>C homozygote (VUS)
49	M	5.0	No	-	Yes	-	272,00	195,00	Diet+omega 3	LDLR	C.1618G>A heterozygote, c.1060+7T>C homozygote (VUS)
50	M	11.0	No	-	No	-	281,00	195,00	Diet	NA	
51	F	3.0	Yes	-	No	-	254,00	198,00	Diet	NA	
52	F	10.0	No	-	Yes	-	259,00	198,00	Diet+omega 3	Undetected	
53	F	7.0	Yes	-	Yes	+	271,00	198,00	Diet	NA	
54	M	4.0	No	-	Yes	-	279,00	204,00	Diet	NA	
55	F	5.0	No	-	Yes	-	287,00	210,00	Diet+omega 3	NA	
56	F	3.0	Yes	-	No	-	296,00	211,00	Diet	NA	
57	M	12.0	Yes	-	No	-	298,00	213,00	Diet+statin	LDLR	c.694+2T>C heterozygote
58	F	13.0	No	-	Yes	-	316,00	217,00	Diet	Undetected	
59	F	7.0	No	-	No	-	280,00	219,00	Diet	NA	
60	M	11.0	No	-	No	-	306,00	221,00	Diet	NA	
61	M	12.0	No	-	No	-	323,00	221,00	Diet+statin	NA	
62	F	14.0	No	-	Yes	+	291,00	229,00	Diet+omega 3+statin	LDLR	c.245G>A / c.343C>T compoundheterozygote
63	M	4.0	No	-	Yes	-	307,00	231,00	Diet	NA	
64	F	9.0	No	-	Yes	+	317,00	246,00	Diet+statin	NA	
65	M	10.0	No	-	Yes	+	321,00	246,00	Diet+statin	NA	
66	F	12.0	Yes	-	Yes	-	305,00	250,00	Diet+statin	LDLR	c.2139A>G heterozygote
67	F	8.0	Yes	-	No	-	322,00	252,00	Diet+statin	NA	
68	M	9.0	Yes	-	No	-	303,00	257,00	Diet+omega 3+statin	LDLR	c.418G>A heterozygote

69	M	11.0	Yes	-	No	-	332,00	259,00	Diet+statin	LDLR	c.1102T>G heterozygote
70	M	1.0	No	-	Yes	+	326,00	262,00	Diet+omega 3	LDLR	c.1867_1869delATC heterozygote
71	F	15.0	No	-	No	-	345,00	264,00	Diet+statin	NA	
72	F	13.0	No	-	Yes	+	358,00	264,00	Diet+statin	LDLR	c.1867_1869delATC heterozygote
73	F	16.0	No	-	Yes	+	350,00	267,00	Diet+omega 3+statin	LDLR	c.1102T>G heterozygote
74	F	15.0	Yes	-	No	-	341,00	268,00	Diet+statin	NA	
75	M	10.0	No	-	Yes	+	341,00	280,00	Diet+statin	LDLR	c.2215C>T heterozygote
76	M	3.0	No	-	Yes	+	358,00	282,00	Diet+omega 3	LDLR	c.1729T>C heterozygote
77	M	12.0	No	-	No	-	334,00	289,00	Diet+omega 3+statin	NA	
78	M	10.0	Yes	-	No	-	374,00	292,00	Diet+statin	LDLR	c.1729T>C heterozygote
79	M	13.0	No	-	No	-	376,00	295,00	Diet+statin	LDLR	c.1856T>G heterozygote
80	M	8.0	Yes	-	No	-	346,00	296,00	Diet+statin	LDLR	c.2359G>A heterozygote
81	F	15.0	No	-	Yes	+	387,00	303,00	Diet+statin	LDLR	c.1646G>A heterozygote
82	F	5.0	No	-	Yes	-	370,00	305,00	Diet	NA	
83	M	10.0	No	-	Yes	-	370,00	318,00	Diet+omega 3+statin	NA	
84	F	8.0	No	-	Yes	-	391,00	331,00	Diet+omega 3	LDLR	c.693C>A heterozygote
85	M	6.0	Yes	-	No	-	386,00	367,00	Diet+statin	LDLR	c.1171G>A heterozygote
86	F	10.0	Yes	-	No	-	418,00	395,00	Diet+statin	Undetected	
87	M	7.0	Yes	-	Yes	-	410,00	397,00	Diet+omega 3+statin	NA	
88	F	10.0	No	-	No	-	499,00	410,00	Diet+statin+ezetimib	LDLR	c.940G>A heterozygote
89	F	3.0	No	-	Yes	-	482,00	439,00	Diet+omega 3	NA	
90	F	9.0	No	-	No	-	557,00	493,00	Diet+statin+ezetimibe	LDLR	c.71dup homozygote
91	F	10.0	Yes	-	Yes	-	626,00	571,00	Diet+statin+ezetimibe+apheresis	LDLR	c.826T>C homozygote
92	M	13.0	Yes	-	Yes	-	660,00	597,00	Diet+statin+ezetimibe	LDLR	c.2389+5G>T homozygote
93	F	6.0	No	-	No	-	760,00	659,00	Diet+statin+ezetimibe	NA	

94	M	1.0	No	-	No	-	841,00	747,00	Diet	Undetected	
95	F	16.0	No	-	Yes	-	245,00	207,00	Diet	LDRL	c.694+2T>C heterozygote
96	F	6.0	No	-	No	-	322,00	237,00	Diet	NA	
97	F	9.0	No	-	Yes	-	377,00	286,00	Diet+statin	LDRL	c.2416dup heterozygote
98	M	1.5	Yes	-	No	-	538,00		Diet	NA	
99	F	4.5	Yes	-	No	-	204,00	132,00	Diet	NA	
100	M	15.0	No	-	Yes	-	208,00	149,00	Diet	NA	
101	F	7.5	Yes	-	Yes	-	231,00	164,00	Diet+statin	NA	
102	M	5.0	No	-	Yes	-	263,00	167,00	Diet	NA	
103	M	2.0	No	-	Yes	-	263,00	167,00	Diet	NA	
104	F	8.5	No	-	No	-	280,00	171,00	Diet	Undetected	c.2635G>C heterozygote
105	F	16.5	Yes	-	No	-	264,00	184,00	Diet	LDLR	c.761A>C heterozygote
106	F	14.5	Yes	-	Yes	+	282,00	197,00	Diet+statin	NA	
109	F	16.0	No	-	No	-	333,00	213,00	Diet	NA	
108	M	10.0	Yes	-	No	-	301,00	221,00	Diet	NA	
109	M	1.0	Yes	-	Yes	-	325,00	238,00	Diet	LDLR	c.1729T>C heterozygote
110	M	8.0	Yes	-	No	-	304,00	239,00	Diet+statin	NA	
111	M	16.0	Yes	-	No	-	307,00	253,00	Diet	NA	
112	F	16.0	Yes	-	Yes	-	335,00	263,00	Diet+statin	NA	
113	M	13.0	Yes	-	Yes	+	221,00	145,00	Diet	LDLR	c.1720 C>T heterozygote
114	M	7.0	No	-	Yes	-	255,00	181,00	Diet	LDLR	c.1729T>C heterozygote
115	M	3.0	No	-	Yes	-	243,00	158,00	Diet	Undetected	
116	F	4.0	No	-	No	-	271,00		Diet+statin	LDLR	c.1729T>C heterozygote
117	M	2.0	No	-	Yes	-	344,00	257,00	Diet+statin	LDLR	c.1729T>C heterozygote
118	M	1.0	No	-	Yes	-	302,00	224,00	Diet	LDLR	c.1729T>C heterozygote

119	M	8.0	No	-	Yes	-	341,00	260,00	Diet+statin	NA	
120	F	8.0	No	-	Yes	+	209,00		Diet+statin	NA	
121	F	4.0	No	-	Yes	+	381,00	297,00	Diet+statin	LDLR	c.1729T>C heterozygote
122	F	7.0	Yes	-	No	-	305,00	249,00	Diet+statin	LDLR	c.415 G>A heterozygote
123	M	14.0	Yes	-	No	-	252,00	193,00	Diet+statin	LDLR	c.2044 C>T heterozygote
124	F	10.5	No	-	No	-	377,00	300,00	Diet+statin	LDLR	c.2093 G>T heterozygote

Abbreviations: M: male; F: female; MI: myocardial infarction; NA: not available

Clinical findings

There were no complaints at the time of diagnosis in 81.5% of the cases, xanthomawas present in 4 (3.2%), and there were overweight complaints in 5 (4%). The complaints of the cases on presentation are shown in Table 1.

Table I: Complaints of the patients at the time of diagnosis

Complaint	Number of cases	Percentage rate (%)
Overweight-obesity	5	4
Xanthomas	4	3.2
Upperrespiratorytractinfection	3	2.4
Chestpain	2	1.6
Transaminaseelevation	1	0.8
Menstrualirregularity	1	0.8
Polydipsia-pollakiuria	1	0.8
Weakness	1	0.8
Shortstature	1	0.8
Hypoglycemia	1	0.8
Abdominalpain	1	0.8
Skin rash	1	0.8
Vomiting	1	0.8
Withoutcomplaint	101	81.5

During diagnosis and follow-up, xanthoma of various dimensions were determined in 7 (5.6%) cases, hepatomegaly in 3 (2.4%), and hepatosteatosis in 7 (5.6%). Thickening of the carotid intima media was determined in 4 (3.2%) cases and coronary artery disease in 2 (1.6%). One of these two cases died at the age of 23 years.

At the time of diagnosis, the mean TC levels of the cases were determined to be 339±142 mg/dl (195–1016), LDL-C: 254±110 mg/dl (132–747), HDL-C: 58±21 mg/dl (3–190), and triglycerides: 105±72 mg/dl (41–494). Mean glucose levels were 86.0±8.2 mg/dl, AST: 26.0±8.3 U/L, and ALT: 15.0±7.3 U/L.

Differences between cases with heterozygote familial hypercholesterolemia (HeFH) and those with homozygote familia hypercholesterolemia (HoFH) – including compound heterozygote- in respect of TC and LDL-C levels at the time of diagnosis were evaluated with the Mann Whitney U-test as the data did not show normal distribution. The values of the HoFH group were determined to be significantly higher ($p<0.001$ and $p=0.028$).

Genetic findings

Given the limited accessibility of genetic testing facilities in Türkiye, genetic analysis was performed in 74 of the 124 cases (59.7%) included in the study. Of these cases, a pathogenic variant was determined in 63/74 (85.1%), as a variant in the LDLR gene in 60/63 (95.2%), in the APOE gene in 2/63 (3.2%), and in the APOB gene in 1/63 (1.6%).

In the 35 different variants determined in 68 alleles in the LDLR gene, a heterozygote variant was determined in 52/60 (86.7%), a homozygote variant in 7/60 (11.7%), and a compound heterozygote variant in 1/60 (1.6%). The most common variant determined was c.1729T>C (p.Trp577Arg) (30.8% – n:21/68). Other variants determined in the LDLR gene are shown in Figure 1. In 2 cases, c.1060+7T>C variant was determined in homozygote form in the LDLR gene. In the pathogenity scoring this was reported as a variant of uncertain significance. In both cases heterozygote c.1502C>T and c.1618G>A variants were also determined to be pathogenic. Consistent with the laboratory findings, these two cases were accepted as heterozygote familial hypercholesterolemia. Other variants are listed in Supplementary material 1.

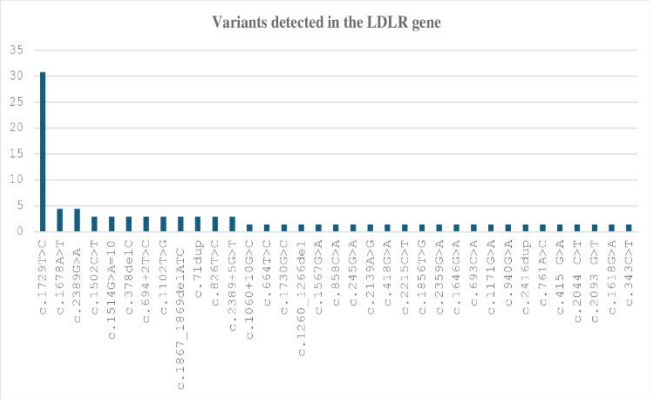

Figure 1. Frequency of variants detected in the LDLR gene

In 2 cases, c.500-502DelTCC and c.388T>C variants in the APOE gene were determined as heterozygote. In 1 case, c.7890G>C variant in the APOB gene was determined to be heterozygote.

Management

The treatments applied were seen to be 46/124 (37.1%) diet treatment, 12/124 (9.7%) diet+omega3, 7/124 (5.6%) diet+omega3+statins, 45/124 (36.3%) diet+statins, 4/124 (3.2%) statins only, 4/124 (3.2%) diet+statins+ezetimibe, and 3/124 (2.4%) diet+statins+ezetimibe+LDL apheresis, and no treatment in 3/124 (2.4%). Of the 117/124 (94.4%) cases who were recommended to follow diet treatment, adherence to the diet was not good in 66 (56.4%).

Decreases in TC and LDL-C levels post-treatment compared to before treatmentwere determined to be 15.4% and 17.8%, respectively in cases not taking pharmacotherapy, 25.7% and 32.4% in cases using statins only, and 44.7% and 47.9% in cases using statins +ezetimibe.

Liver transplantation was performed in two siblings who had a homozygote variant in the LDLR gene for which diet+statins treatment was not effective and LDL apheresis could not be performed. In one of the siblings, liver transplantation from a healthy donor was performed at the age of 3 years, and in the other, as a healthy living donor could not be found, liver transplantation was performed from the heterozygote mother on the family's request when the patient was 3.5 years old and had widespreead xanthoma.

LDL apheresis was applied to 3 cases in this study, all of whom had homozygote variants in the LDLR gene. Of these, 2 patients did not attend LDL apheresis treatment regularly, and 1 attended regularly once every 1-2 weeks.

DISCUSSION

Demographic findings

A previous study in Japan reported the frequency of HeFH as 1/300, and it was also reported that FH was present in 1/30 patients with coronary artery disease (CAD) and in 1/15 patients with premature CAD[6].Pederiva et al. stated that diagnosis and treatment of FH in the general population remained insufficient[12]. Although the current study was multicentre in design, it does not provide information about the general incidence in Türkiye. A previous

study in Türkiye reported the frequency of FH as 1/270 in children and adolescents, and as 1/164 in the general population[13].

Clinical findings

In most patients who have not started treatment and have very high LDL-C levels, evident atherosclerosis develops before the age of 20 years and they generally die before the age of 30 years[5]. The risk of early atherosclerotic cardiovascular disease (ASCVD) in adults with FH aged 20-39 years is 100-fold greater than in individuals of the same age without FH[14]. It is known that when atherosclerosis starts in the early periods of life, it gradually progresses and leads to clinical symptoms in later stages of life. Both autopsy studies and imaging studies have shown the presence of atherosclerosis in adolescents and young adults[15]. Consistent with this, there was determined to be carotid intima media thickening and atherosclerotic changes in the coronary artery in the current study cases.

Heterozygote phenotype generally emerges with tendon xanthoma and the homozygote phenotype with both tendon and skin xanthoma[3].In the current study, xanthoma were determined in 5.6% of the cases. In one case determined with homozygote (LDLR) hypercholesterolemia at the age of 1.5 years, there was noticed to be an orange-yellow colour change in lines on the palm of the hand at the age of approximately 2 years, and xanthoma started to emerge within the following 6 months.

HoFH is characterised by accelerated atherosclerosis. The first signs and symptoms in young children are usually associated with aorta narrowing and insufficiency[5]. Patients with homozygote or compound heterozygote FH usually present in the first 10 years of life with a severe and variable clinical status[16]. Untreated LDLR-negative HoFH patients rarely survive beyond the second decade[5]. In literature, 3 cases have been reported who were exitus at 4-6 years of age[10,11,17]. In the current study, one patient with homozygote hypercholesterolemiaincompatible with treatment was exitus at the age of 23 years.

Diagnostic process

For FH diagnosis, the primary criteria employed include the US Make Early Diagnosis to Prevent Early Death (MEDPED) criteria, the UK Simon Broome system (UK FH Register criteria), the Dutch Lipid Clinic Network guidelines, and the National Lipid Association expert panel's guidance[2,18]. However, regardless of the criteria, genetic analyses constitute an indisputable central part of diagnosis of all types[19].

As LDL levels may be hidden by high HDL in HeFH, screening should be started after the first 6 weeks of life to avoid false negative results. With the exception of the adolescent years when growth spurts occur, LDL-C levels are expected to be high in FH throughout childhood and adulthood[20]. Among the patients in the present study, 14 (11.2%) were diagnosed at the age of 2 years or below. Of these cases, FH was determined with selective family screening in 10, with universal screening in 2, and incidentally because of other complaints in[2].

The European Atherosclerosis Society (EAS) recommends screening at 5 years of age, and has stated the following criteria for paediatric FH: (i) LDL-C>190 mg/dl, (ii) LDL-C>160 mg/dl and one parent with premature CAD or hyper-LDL-C, (iii) LDL-C>130 mg/dl and the determination of a pathogenic gene mutation in the patient or one of the parents.6 In the current study, there were 24 cases with LDL-C levels of 130-190 mg/dl at the time of diagnosis. There was no diagnosis of hypercholesterolemia in the parents of 6 (25%) of those 24 cases, and the diagnosis could be established genetically in 8 (33.3%). Additionally, LDL-C levels were found to be above 500 mg/dl in 5 cases at the time of

diagnosis. Of these,homozygote (LDLR) FH was determined in 4 and heterozygote (LDLR) in only one.

Genetic testing

The rate of determining pathogenic variants in FH cases diagnosed clinically has been reported to be 60-80% in adults.6 In patients where mutation cannot be determined, hypercholesterolemia may be secondary to genetic abnormalities that cannot be identified because of limitations in the method used, or it may be polygenic in nature.7,18 In this case series, apathogenic variant could be determined in 85.1% of the cases for which genetic analysis could be performed, which was consistent with the literature.

FH linked to APOB, LDLR, and PCSK9 follows an autosomal dominant mode of inheritance.2 The HoFH diagnosis is confirmed with the identification of two pathogenic mutations in two loci in the gene causing FH (LDLR, PCSK9, APOB). The identification of two loci of two pathogenic mutations in LDLRAP1 leads to a diagnosis of autosomal recessive hypercholesterolemia.6 Loss-of-function variants in the LDLR gene account for 60-80% of the FH phenotype in patients. This is followed by variants in the APOB gene (5-10%) or gain-of-function variants in PCSK9 (<1%). Occasionally, variants can occur in the APOE gene or associated with one of a largegene group(LDLRAP1, LIPA, SCAP, GPIHBP1, or STAP1).19 In the current study, variants were determined in the LDLR, APOB, and APOE genes, primarily at a high rate in the LDLR gene, consistent with the literature. No variants were determined in the PCSK9 or LDLRAP1 genes.

Screening

Hypercholesterolemia screening should be based onphenotype via LDL-C measurement through cascade screening of high-risk paediatric patients based on family history, or selective screening, or genetic testing when possible. In terms of age, it is recommended to screen as early as 2 or 5 years old, according to the National Heart, Lung, and Blood Institute (NHLBI) in the United States and the EAS guidelines, respectively.3 Routine universal lipid screening is recommended by the NHLBI for children at 11 years of age, and if there is a first-degree relative history of ASCVD or FH, it is suggested that it can be performed as early as 12 months[21]. In another publication, screening below the age of 2 years is not recommended as lipid and lipoprotein levels tend to increase up to approximately 2 years and become stable thereafter[4]. If we had been able to conduct screening in light of the guidelines' recommendations, early diagnosis and treatment before the age of 11 would have been possible in 37 out of 124 (29.8%) cases.

MANAGEMENT

Lifestyle changes

Given their critical role in brain development, lipids should not be limited in infants below 12 months of age unless deemed medically essential[22]. Diet treatment for children is generally recommended to be started after the age of 2 years[3].

Of the daily energy requirement, 20-25% should be provided by fats and 50-60% by carbohydrates. Saturated fats should not exceed 7% of the energy requirement, and daily cholesterol consumption should not exceed 200 mg. Trans-fats should be reduced as much as possible[6,22]. In the current study, diet treatment was recommended for 94.4% of the cases, but successful adherence to this treatment was observed to be low.

Pharmacotherapy

In children with hypercholesterolemia, if LDL-C continues to be ≥180 mg/dl despite interventions for lifestyle modification, it is recommended that irrespective of gender drug treatment is started at 8-10 years and the target

is to maintain LDL-C <135 mg/dl[6]. Even in children <10 years of age, if LDL-C is ≥200 mg/dl despite diet and exercise, then an early start to drug treatment should be considered taking age, risk factors, and family history into account[6].

There are data in the literature that the following can be used in hypercholesterolemia treatment: statins7,20, ezetimibe23, PCSK9 inhibitors20,23, angiopoietin-like protein 3 (ANGPTL3) inhibitors24,25, bile acid sequestrants3,23, lomitapide16, bempedoic acid18, mipomersen5,23, niacin23, fibrates20,23, thyroid hormone receptor agonists20, and cholesteryl ester transfer protein inhibitors[20].

Until a sufficient response is obtained in the treatment of FH, ezetimibe, PCSK9 inhibitor (evolocumab), ATP citrate lyase inhibitor (bempedoic acid), ANGPTL3 inhibitor (evinacumab), and LDL apheresis can be applied in addition to statins.26 In the report by Mansfield et al., a case of HoFH (LDLR) treated at 2 years of age showed a 77% reduction in LDL-C levels after starting atorvastatin, ezetimibe, evolocumab, and evinacumab[17]. In the current study, 50.7% of the cases used statins, and 5.6% statins+ezetimibe. In this case series, it was observed that medical treatment, particularly the combination of statins and ezetimibe, was very effective. The decrease in LDL-C level was determined to be 17.8% in cases not taking pharmacotherapy, 32.4% in cases using statins only, and 47.9% in cases using statins +ezetimibe. This suggested that the statins+ ezetimibe treatment was more effective than statins alone.

Lipoprotein apheresis (LA)

There are many reports showing that lipoprotein apheresis treatment provides long-term positive outcomes including regression of skin and tendon xanthoma[6,27], a reduction in angina pectoris symptoms, and suppresses the development of atherosclerotic deposits in the coronary arteries[6]. As HoFH does not generally respond well to drugs, LA treatment is required in most cases. LA is usually started at age 4-6 years, but it has also been reported that it can be performed at 2-4 years[6,11,28]. When LA therapy is delayed in HoFH, mortality from myocardial infarctus has been reported.6 In the current study, LA could only be performed in 3 HoFH cases. Of these, 2 siblings did not attend regularly for LA treatment, so the target LDL-C levels could not be reached and no shrinking of xanthoma was observed.

Surgical Therapy

As the provision of new LDL receptors with liver transplantation increases receptor activity to close to 60% and reduces LDL-C plasma levels by 80%, liver transplantation seems to be a good option forHoFH patients[20]. While liver transplantation is generally preferred from a donor without FH, it has been reported that liver transplantation has been performed from parents with HeFH when a suitable donor cannot be found. However, these patients have to continue with cholesterol-lowering drugs[29]. In one of the current cases, recovery was obtained with liver transplantation from a healthy living donor. The other case, where liver transplantation was performed from the HeFH mother, is being followed up in remission with medical treatment.

CONCLUSION

The findings of this study highlight the importance of routine screening recommendations for hypercholesterolemia in facilitating early case detection. It was also seen that the combination of statins + ezetimibe, which can be used for hypercholesterolemia in Türkiye can be used effectively in this patient group. It has been observed, however, that accessing and routinely performing lipid apheresis remains challenging for HoFH

patients who cannot undergo liver transplantation

Ethics Committee Approval: Ethical clearance for the research was granted by the Local Ethics Committee (Protocol no: 2024/08-48, dated: 23 May 2024). This study was managed accordingly with the Declaration of Helsinki. Because the study had a retrospective design, no informed consent was required from the legal guardians of the cases.

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