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Evaluation of the Frequency of Familial Hypercholesterolemia: A Single-Center Experience

Ailesel Hiperkolesteroleminin Sıklığının Araştırılması: Tek Merkez Deneyimi

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Abstract

Objective: Familial hypercholesterolemia is an autosomal dominant disease associated with elevated low-density lipoprotein cholesterol and increased premature atherosclerosis. In the general population, the frequency of familial hypercholesterolemia has been calculated to be between 1/500-1/200. Although the frequency of familial hypercholesterolemia belonging to different countries has been elaborately reported, the data from Turkey remains insufficient. We aimed to determine the frequency and characteristics of familial hypercholesterolemia in patients from Turkey by screening and analyzing the low-density lipoprotein cholesterol data.

Material and Methods: Between May 2017-May 2018, 20151 laboratory records from individuals elaborately admitted to outpatient clinics for any reason were screened retrospectively, and 430 patients with low-density lipoprotein cholesterol levels ≥190 mg/dL were included in the study.

Results: We observed a secondary cause (secondary hyperlipidemia, the SH group) in 163 patients and familial hypercholesterolemia in 267 patients (1.32%, the familial hypercholesterolemia group) in patients representing our population. The ratio of female to male participants was higher (76.4% vs. 58.4%) and their mean age was significantly higher in the SH group than in the familial hypercholesterolemia group (56.8±13.6 vs 47.1±17.0 years; both p<0.001). Total cholesterol and triglyceride concentrations were higher in the SH group compared to those in the familial hypercholesterolemia group (319.6±65.1 vs 306.8±57.6 mg/dL, p=0.003, and 436.8±308.8 vs 136.0±55.9 mg/dL, p<0.001, respectively). There was no difference between the two groups in terms of atherosclerotic diseases.

Conclusion: The frequency of familial hypercholesterolemia (1/76) in the region we studied was higher than in other societies. Therefore, the diagnosis of familial hypercholesterolemia should be considered in subjects with low-density lipoprotein cholesterol above 190 mg/dL, especially in young males. Early diagnosis is especially important for the prevention of adverse cardiovascular events in patients and their family members.

Keywords: Familial hypercholesterolemia; Dutch lipid network criteria; low-density lipoprotein cholesterol

Özet

Amaç: Ailesel hiperkolesterolemi düşük yoğunluklu lipoprotein kolesterol yüksekliği ve erken ateroskleroz ile karakterize olan otozomal dominant geçişli bir hastalıktır. Genel popülasyondaki sıklığının 1/500-1/200 arasında olduğu tahmin edilmektedir. Değişik toplumlardaki sıklığına dair veriler olmasına rağmen Türkiye'deki durum bilinmemektedir. Bu çalışmada, Türkiye'deki hastalara ait düşük yoğunluklu lipoprotein kolesterol verilerinin taranarak ailesel hiperkolesterolemi sıklığını ve özelliklerini saptanmaya çalışılması amaçlanmıştır.

Gereç ve Yöntemler: Mayıs 2017-Mayıs 2018 tarihleri arasında herhangi bir nedenle ayaktan hastaneye başvuran kişilere ait 20.151 laboratuvar kaydı incelendi ve düşük yoğunluklu lipoprotein kolesterolü 190 mg/dL ve üzeri olan toplam 430 hasta çalışmaya dâhil edildi.

Bulgular: Yüz altmış üç hastada sekonder bir neden (sekonder hiperlipidemi, SH grup) ve 267 hastada ailesel hiperkolesterolemi (%1,32, ailesel hiperkolesterolemi grup) saptandı. Kadın cinsiyet sıklığı (%76,4'e karşı %58,4) ve ortalama yaş (56,8±13,6'ya karşı 47,1±17,0 yıl) SH grubunda ailesel hiperkolesterolemi grubuna göre anlamlı yüksekti (her iki p<0,001). Total kolesterol ve trigliserid düzeyleri ailesel hiperkolesterolemi grubu ile karşılaştırıldığında, SH grubunda anlamlı olarak daha yüksek idi (sırasıyla 319,6±65,1'e karşı 306,8±57,6 mg/dL, p=0,003, ve 436,8±308,8'e karşı 136,0±55,9 mg/dL, p<0,001). İki grup arasında aterosklerotik hastalıklar açısından fark bulunmadı.

Sonuç: ailesel hiperkolesterolemi sıklığı (1/76) çalışmayı yaptığımız bölgede diğer toplumlardan daha sık bulundu. Bu nedenle, düşük yoğunluklu lipoprotein kolesterolü 190 mg/dL'nin üstünde olan özellikle genç erkeklerde ailesel hiperkolesterolemi tanısı akılda bulundurulmalıdır. Erken tanı, hem hastada hem de ailesinde oluşabilecek özellikle istenmeyen kardiyovasküler olaylardan korunma için önemlidir.

Anahtar kelimeler: Ailesel hiperkolesterolemi, Dutch lipid network kriterleri, düşük yoğunluklu lipoprotein içeren kolesterol

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Introduction

Familial hypercholesterolemia (FH) is an inherited disorder characterized by increased plasma low-density lipoprotein cholesterol (LDL-C) level and premature atherosclerotic cardiovascular disease (ASCVD) (1,2). FH is presented with homozygous or heterozygous forms of genes encoding LDL receptor, apolipoprotein B or proprotein convertase subtilisin/Kexin type 9 (1,2). Classically, the defect in the LDL receptor pathway leads to decreased clearance of LDL-cholesterol from plasma resulting in an increase in the plasma LDL concentration (2). In homozygous cases, LDL-C level is greater than 400-500 mg/dL while in heterozygous cases it has been reported in a range of 190-400 mg/dL (3). FH has been reported at varying frequencies (1/500-1/200) in different societies (4). However, currently, there are no data on the frequency of FH from Turkey.

Currently, there are various clinical criteria for the diagnosis of FH based on physical examination, plasma LDL-C levels and family history (5). The most popular is the Dutch Lipid Network Criteria that evaluates the presence of premature coronary artery disease, peripheral or cerebral vascular disease in the patient and his family, the presence of tendon xanthoma or arcus cornealis on physical examination, and raised LDL-C levels (5). The likelihood of FH is determined by the Dutch Lipid Network Criteria involving a clinical examination, family history, level of LDL-cholesterol and evaluation of genetic tests. The scores of analyses were categorized as >8, definite FH; 6-8, probable FH; 3-5, possible FH; <3, unlikely FH (Table 1) (5).

We determined the frequency of FH patients in our region by examining the hospital records. The cases with LDL-C values above 190 mg/dL were conferred 3 points and a "possible" diagnosis of FH as per the Dutch Lipid Network Criteria.

Patients and Protocols

Between May 2017 and May 2018, 20151 cases admitted to the outpatient clinics of Harran University Hospital for any reason were examined and their plasma cholesterol levels were evaluated retrospectively. A total of 430 patients, including those using antilipidemic drugs with LDL-C level ≥190 mg/dL, were included in the study. The ethics committee of Harran University approved the study protocol on 7th June 2018 (protocol number: 6/27), as per the ethical principles for human investigations, outlined by the Helsinki Declaration. The patients who had a secondary condition such as diabetes mellitus, hypothyroidism, acute hepatitis, end-stage renal failure, and the nephrotic syndrome were categorized into the secondary hyperlipidemia (SH) group and others were categorized into the FH group. According to the Dutch Lipid Network Criteria (Table 1), the patients who had LDL-C above 190 mg/dL were given three points and were accepted as "possible" FH cases. Pregnant women were excluded from the study.

Serum total cholesterol, LDL-C, HDL-C and triglyceride levels were estimated using the Abbott C16000 autoanalyzer device using the colorimetric method.

Overall data were presented as mean (minimum and maximum values), while for intergroup comparisons the data were presented as mean±standard deviation. Categorical data were presented as n (%). SPSS version 20.0 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analyses. Normalized data were evaluated by the Kolmogorov-Smirnov test. Student's t-test for normally distributed data and Mann-Whitney U test for data not showing normal distribution were used. Categorical variables were compared using the chi-square test. Two-tailed P value <0.05 was considered to be significant.

Results

Among 430 patients with hypercholesterolemia, 280 (65.1%) were females and 150 (34.9%) were males, with an average age of 50.8 (0-88) years. On average, female patients were older than male patients ($p<0.001$). One hundred and sixty-three patients with secondary conditions were included in the SH group, and the other 267 patients were included in the FH group. The rates of secondary causes were diabetes mellitus (n=121, 74.2%), hypothyroidism (n=23, 14.1%), nephrotic syndrome (n=9, 5.5%), acute hepatitis (n=5, 3.1%), and end-stage renal failure (n=5, 3.1%). According to the Dutch lipid scoring system, 238 patients received 3 points, 23 patients

Table 1. The dutch lipid network diagnostic criteria.

Criteria	Score*
Family History	
First-degree relative with premature+ coronary and/or vascular disease, or a first-degree relative with known LDL-cholesterol ≥95th percentile for age and sex	1
First-degree relative with tendon xanthomata and/or arcus cornealis, or children aged ≤18 years with known LDL-cholesterol ≥95th percentile for age and sex	2
Clinical History	
Patient with premature+ coronary artery disease	2
Patient with premature+ cerebral or peripheral vascular disease	1
Physical Examination	
Tendon Xanthomas	6
Arcus cornealis at age ≤45 years	4
LDL Cholesterol (mg/dL)	
≥330	8
250-329	5
190-249	3
155-189	1
DNA Analysis	
Functional mutation of LDLR, APOB, and PCSK9	8

+; men ≤55 years, women≤60 years; * ; Score ≥8: "Definite Familial Hypercholesterolemia",; Score 6-7: "Probable Familial Hypercholesterolemia", ;Score 3-5: "Possible Familial Hypercholesterolemia"; Score <3: "Unlikely Familial Hypercholesterolemia".
APOB: Apolipoprotein-B; LDLR: LDL receptor; PCSK9: Proprotein convertase subtilisin/kexin type 9.

received 5 points and 6 patients received 8 points. The rate of FH occurrence was 13.2 in 1000 (1/76) in our population.

On assessing the gender ratio, the number of females in the SH group (76.1%) was higher than in the FH group (58.4%) ($p<0.001$). SH group had a greater number of older patients than in the FH group ($p<0.001$). Total cholesterol and triglyceride levels in the SH group were significantly higher than in the FH group ($p=0.003$ and $p<0.001$, respectively). Clinical and biochemical data of the groups are presented in Table 2.

In the FH group, we detected hypertension in 17 (6.3%) patients, cerebrovascular disease in 11 (4.1%) patients, coronary artery disease in 32 (12.0%) patients, and peripheral arterial disease in one (0.3%) patient. In the SH group, 11 (4.1%) patients had hypertension, one (0.5%) patient had a cerebrovascular disease and 26 (15.9%) patients had coronary artery disease. Although the FH group was younger, the frequency of atherosclerotic diseases was similar in both groups ($p>0.05$).

Discussion

FH is a single gene disorder causing morbidity and mortality at an early age (1,5). Moreover, shortened life-span due to mortal ASCVD may occur in untreated subjects (6). FH was found to be prevalent at different rates in various populations (5). For instance, the prevalence of FH was 1/500 in European countries, 1/270 in Canada and 1/500 in the USA, as high as 1/85 in the Middle East (Lebanon), 1/72 in African-origin subjects and 1/67 in the Askenazi Jews in South Africa, while as low as 1/900 in Japan (7-13). We evaluated the frequency of FH in Sanliurfa Provience of Turkey, for which no previous data are available, and found the rate to be 1/76. Our study considered only LDL-C levels and only included individuals with "possible" FH. It is plausible that some patients had been taking antilipidemic agents during the screening period, and thus were not included because of low LDL-C levels. The probability of FH is drastically increased in patients with LDL-C above 190 mg/dL (14). Additionally, according to the Dutch Lipid Network criteria, a subject

Table 2. The comparison of clinical and laboratory parameters between the groups.

Parameter	FH group (n=267)	SH group (n=163)	p-value
Gender (female/male)	156/111	124/39	<0.001
Age (year)	47.1±17.0	56.8±13.6	<0.001
Glucose (mg/dL)	99.9±20.7	203.8±124.7	<0.001
Creatinine (mg/dL)	0.77±0.17	1.14±2.60	<0.001
ALT (U/l)	29.8±31.8	34.3±113.5	0.028
TSH (mIU/l)	2.2±1.9	10.6±29.0	<0.001
Total cholesterol (mg/dL)	306.8±57.6	319.6±65.1	0.003
LDL-C (mg/dL)	219.5±49.4	222.3±49.9	NS
HDL-C (mg/dL)	48.3±13.1	49.5±16.2	NS
Triglyceride (mg/dL)	136.0±55.9	436.8±308.8	<0.001
Hypertension (n (%))	17 (6.3%)	11 (4.1%)	NS
Cerebrovascular disease	11 (4.1%),	1 (0.5%)	
Coronary artery disease	32 (12.0%)	26 (15.9%)	
Peripheral arterial disease	1 (0.3%)	-	

ALT: Alanine aminotransferase; FH: Familial hyperlipidemia; HDL-C: High-density lipoprotein containing cholesterol; LDL-K: Low-density lipoprotein containing cholesterol; NS: Nonsignificant; SH: Secondary hyperlipidemia; TSH: Thyroid stimulant hormone.

with LDL-C level above 155 mg/dL is a potential FH candidate when evaluated for familial history, and clinical and physical examination (15). Although the present study showed a high prevalence of FH in our population, it may not represent the real frequency because other diagnostic criteria were not evaluated. According to the Turkish Statistical Institute, the overall frequency of consanguineous marriages in Turkey is 20.9%, while its Southeastern Anatolia Region, where the study was conducted, has the most frequent consanguineous marriages at 40.4% (16). A high percentage of consanguineous marriages in our region could explain high FH prevalence there. Notwithstanding, our results were obtained from a single tertiary center and cannot be adapted to the general population. In a similar study from a tertiary hospital in Australia, Mirzaee et al. screened 4943 lipid profiles and found high FH incidence at 1/50 in patients with LDL values above 4.9 mmol/L (190 mg/dL) (17).

The primary laboratory and clinical findings in FH are LDL-C elevations, early ASCVD, and accumulation of cholesterol under the skin (xanthoma) and around the peripheral cornea (arcus cornea) (6). To diagnose FH, the secondary causes such as hepatic, renal and thyroid dysfunction should be excluded. In FH, LDL-C levels are above 90th percentile according to age and gender, while triglyceride and HDL-C are generally in the normal range (6). In our study, the mean triglyceride level was also in normal range in the FH group and higher than 150 mg/dL in the SH group.

The risk of cardiovascular events is 20 times more in FH patients without treatment (14). ASCVD sets in before the age of 20 years in untreated homozygous individuals, and at around 35 years in untreated heterozygous individuals (18). Likewise, 50% of 50-year-old men and 30% of 60-year-old women with FH have ASCVD (19,20). In this patient group, 5 to 10-fold increase in the risk of peripheral arterial disease was observed (21,22). Although the mean age was below 50 in our FH group, the prevalence of known atherosclerotic vascular disease was 16.1% (cerebrovascular disease 4.1% and coronary artery disease 12.0%). Besides, some patients may have been incorrectly evaluated as normal. Another limitation of our study was that we scanned only the hospital patient records and did not interview the patients directly. Nevertheless, the FH group had a similar ASCVD frequency as that of the SH group, although the members of the FH group were significantly younger than those in the SH group.

Conclusion

The frequency of FH was estimated to be high in Sanliurfa Provience. Additionally, the average age of FH patients was less than that of SH patients. Therefore, young individuals with elevated LDL-C level should be especially evaluated as potential FH patients and must be examined for lipid deposits and the presence of atherosclerotic events in their body. Early detection of FH may help prevent ASCVD and associated morbidity and mortality in patients and other members of their family.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Mehmet Ali Eren, Tevfik Sabuncu; Design: Mehmet Ali Eren, Tevfik Sabuncu; Control/Supervision: Tevfik Sabuncu; Data Collection and/or Processing: Ahmet Cebeli Gökay, Ataman Gönel, İsmail Koyuncu; Analysis and/or Interpretation: Mehmet Ali Eren; Literature Review: Ataman Gönel, Mehmet Ali Eren; Writing the Article: Mehmet Ali Eren, Tevfik Sabuncu; Critical Review: Tevfik Sabuncu; References and Fundings: İsmail Koyuncu; Materials: Ataman Gönel.

References

1. Gidding SS, Champagne MA, de Ferranti SD, Defesche J, Ito MK, Knowles JW, McCrindle B, Raal F, Rader D, Santos RD, Lopes-Virella M, Watts GF, Wierzbicki AS; American Heart Association Atherosclerosis, Hypertension, and Obesity in Young Committee of Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and Council on Lifestyle and Cardiometabolic Health. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. Circulation. 2015;132:2167-2192. [Crossref] [PubMed]
2. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab. 2012;97:3956-3964. [Crossref] [PubMed]
3. Gidding SS. Familial hypercholesterolemia: now part of cardiovascular disease genetic epidemiology research. J Am Coll Cardiol. 2016;67:2590-2592. [Crossref] [PubMed]
4. Santos RD, Gidding SS, Hegele RA, Cuchel MA, Barter PJ, Watts GF, Baum SJ, Catapano AL, Chapman MJ, Defesche JC, Folco E, Freiberger T, Genest J, Hovingh GK, Harada-Shiba M, Humphries SE, Jackson AS, Mata P, Moriarty PM, Raal FJ, Al-Rasadi K, Ray KK, Reiner Z, Sijbrands EJ, Yamashita S; International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel: Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. Lancet Diabetes Endocrinol. 2016;4:850-861. [Crossref] [PubMed]
5. Varghese MJ. Familial hypercholesterolemia: a review. Ann Pediatr Cardiol. 2014;7:107-117. [Crossref] [PubMed] [PMC]
6. Safarova MS, Kullo IJ. My approach to the patient with familial hypercholesterolemia. Mayo Clin Proc. 2016;91:770-786. [Crossref] [PubMed] [PMC]
7. Steyn K, Goldberg YP, Kotze MJ, Steyn M, Swanepoel AS, Fourie JM, Coetzee GA, van der Westhuyzen DR. Estimation of the prevalence of familial hypercholesterolaemia in a rural Afrikaner community by direct screening for three Afrikaner founder low density lipoprotein receptor gene mutations. Hum Genet. 1996;98:479-484. [Crossref] [PubMed]
8. Seftel HC, Baker SG, Sandler MP, Forman MB, Joffe BI, Mendelsohn D, Jenkins T, Mieny CJ. A host of hypercholesterolaemic homozygotes in South Africa. Br Med J. 1980;281:633-636. [Crossref] [PubMed] [PMC]
9. Mabuchi H, Haba T, Ueda K, Ueda R, Tatami R, Ito S, Kametani T, Koizumi J, Miyamoto S, Ohta S, Takeda R, Takegoshi T, Takeshita H. Serum lipids and coronary heart disease in heterozygous familial hypercholesterolemia in the Hokuriku District of Japan. Atherosclerosis. 1977;28:417-423. [Crossref] [PubMed]
10. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. Am J Epidemiol. 2004;160:407-420. [Crossref] [PubMed]
11. Moorjani S, Roy M, Gagné C, Davignon J, Brun D, Toussaint M, Lambert M, Campeau L, Blaichman S, Lupien P. Homozygous familial hypercholesterolemia among French Canadians in Quebec Province. Arteriosclerosis. 1989;9:211-216. PMID: 2923577. [Crossref] [PubMed]

12. Goldstein JL, Schrott HG, Hazzard WR, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. J Clin Invest. 1973;52:1544-1568. [Crossref] [PubMed] [PMC]
13. Slack J. Inheritance of familial hypercholesterolemia. Atheroscler Rev. 1979;5:35-66.
14. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, Daniels SR, Gidding SS, de Ferranti SD, Ito MK, McGowan MP, Moriarty PM, Cromwell WC, Ross JL, Ziajka PE; National Lipid Association Expert Panel on Familial Hypercholesterolemia. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5:S1-8. [Crossref] [PubMed]
15. Al-Rasadi K, Al-Waili K, Al-Sabti HA, Al-Hinai A, Al-Hashmi K, Al-Zakwani I, Banerjee Y. Criteria for diagnosis of familial hypercholesterolemia: a comprehensive analysis of the different guidelines, appraising their suitability in the Omani Arab population. Oman Med J. 2014;29:85-91. [Crossref] [PubMed] [PMC]
16. Türkiye İstatistik Kurumu (TÜİK). Aile Yapısı Araştırması 2006. Publication No: 3046. Ankara: Türkiye İstatistik Kurumu Matbaası; 2006;29.
17. Mirzaee S, Choy KW, Doery JCG, Zaman S, Cameron JD, Nasis A. The tertiary hospital laboratory; a novel avenue of opportunistic screening of familial hypercholesterolemia. Int J Cardiol Heart Vasc. 2019;23:100354. [Crossref] [PubMed] [PMC]
18. Horton JD, Cohen JC, Hobbs HH. PCSK9: a convertase that coordinates LDL catabolism. J Lipid Res. 2009;50:S172-177. PMID: 19020338. [Crossref] [PubMed] [PMC]
19. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Familial hypercholesterolemia and coronary heart disease: a HuGE association review. Am J Epidemiol. 2004;160:421-429. [Crossref] [PubMed]
20. Marks D, Thorogood M, Neil HA, Humphries SE. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. Atherosclerosis. 2003;168:1-14. [Crossref] [PubMed]
21. Pereira C, Miname MH, Makdisse MR, Watanabe C, Pesaro AE, Jannes CE, Jannes CE, Kalil Filho R, Pereira AC, Santos RD. Peripheral arterial disease in heterozygous familial hypercholesterolemia. Atherosclerosis. 2015;242:174-178. [Crossref] [PubMed]
22. Hutter CM, Austin MA, Humphries SE. Familial hypercholesterolemia, peripheral arterial disease, and stroke: a HuGE minireview. Am J Epidemiol. 2004;160:430-435. [Crossref] [PubMed]