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UNRAVELLING FAMILIAL DYSLIPIDEMIA IN CHILDHOOD: GENETIC BACKGROUNDS, CLINICAL PATTERS AND THERAPEUTIC IMPLICATIONS

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Dyslipidemia in childhood is a significant, yet underrecognized, risk factor for premature cardiovascular disease. Familial hypercholesterolemia (FH), the most common monogenic form, remains largely undiagnosed in Romania. This study investigated the prevalence, genetic spectrum, and response to lifestyle interventions among pediatric patients with dyslipidemia at the National Institute for Mother and Child Health "Alessandrescu-Rusescu", Bucharest, Romania. A retrospective cross-sectional study (2011–2020) analyzed >3000 lipid profiles from 2413 children; 18.2% had elevated LDL-cholesterol (≥130 mg/dL), most frequently associated with metabolic disorders and obesity. A complementary prospective study (2021–2023) enrolled 20 children with persistent LDL-C elevation; genetic testing identified pathogenic or likely pathogenic variants in 40% (mainly in LDLR, but also APOB and PCSK9). No pathognomonic clinical signs were observed, highlighting the need for systematic screening. After 12 months of lifestyle intervention, children without FH mutations showed greater LDL-C reduction (−18.5%) than those with mutations (−0.6%), underlining the therapeutic challenge of genetic dyslipidemia. Our findings demonstrate a high burden of undiagnosed pediatric dyslipidemia in Romania and provide the first genetic data on FH in this population. Early detection and national screening programs are urgently needed to reduce long-term cardiovascular morbidity and mortality.

Keywords: familial hypercholesterolemia, dyslipidemia, pediatrics, LDL-cholesterol, genetic testing, Romania.

INTRODUCTION

In the medical world, the interest in dyslipidemia is growing since it is one of the risk factors for early cardiovascular disease. Many times, dyslipidemia starts at a young age, in childhood. Accompanied by an unhealthy lifestyle, wrongful food choices (processed food and fast-food), the tendency towards a sedentary lifestyle, could have severe consequences such as coronary disease at a young age (before 50 years)[1–3].

The presence of modifiable and non-modifiable risk-factors in childhood is associated with cardiovascular events in adulthood[4]. This is why approaching cardiovascular risk-factors, including dyslipidemia in childhood, is essential for improving prognosis, in a preventive approach.

A study conducted by the American Pediatric Association in USA in 2013–2014 revealed that only 30% of pediatricians universally screen children aged 9–11 years for dyslipidemia[5]. In Romania, there is no screening program for dyslipidemia in pediatric patients.

There are four dyslipidemia types in pediatric patients: dyslipidemia determined by lifestyle, dyslipidemia as an adverse effect of medication,

genetic dyslipidemia (including familial hypercholesterolemia) and dyslipidemia associated with other medical conditions[6].

Familial hypercholesterolemia (FH) is a genetic dyslipidemia that determines high LDL-cholesterol values from childhood. According to the EUROASPIRE-IV study that evaluated FH prevalence in 24 European countries it is estimated that 8,3%–30% of patients younger than 50 years have FH[7]. If it is not diagnosed and treated, FH leads to heart attacks in 50% of men before the age of 50 and 30% of women before the age of 60[8]. In a study from the USA, approximately 2% of patients with heart attacks at young age had a pathogenic variant of the LDLR gene[9].

Most patients are asymptomatic during childhood and HF is diagnosed when the cardiovascular event occurs[10]. Pediatric patients are rarely diagnosed because clinical signs are scarce and consist of xanthoma, xanthelasma, corneal arch[11].

Most studies recommend screening for FH before adolescence. LDL-cholesterol values suggestive for FH vary among authors from 140 mg/dL to 190 mg/dL[12–15].

Genetic diagnosis for FH implies identification of one of these five main genes: PCSK9, APOB, APOE, LDLR, ATAP1[16,17]. These mutations have an autosomal dominant transmission. There have also been described autosomal recessive mutations such as LDLRAP[17]. Worldwide, more than 1200 LDLR mutations affecting the functional domain of the LDL receptor have been described[18].

The treatment of dyslipidemia starts and is based on lifestyle and dietary interventions. In certain situations, medical treatment is required. Medical treatment options for patients with dyslipidemia and specifically familial hypercholesterolemia include statins, PCSK9-inhibitors, and monoclonal antibodies. Recent data demonstrate that initiating treatment with statins in young individuals under 18 years of age diagnosed with familial hypercholesterolemia reduces the risk for cardiovascular disease in adulthood[4].

Approaching dyslipidemia in pediatric patients, in a preventive manner, can improve their quality of life by preventing cardiovascular events for which they have high risk. A screening program for familial hypercholesterolemia could help avoid 46 heart attacks, 50 cases of angina, 8 cerebral strokes and 16 deaths for every 1000 people tested over a 20 years' timeframe[19].

The work presented in this paper was part of the doctoral thesis of PhD. Dr. Andreea Teodora Constantin, finalized in 2023. Her doctoral thesis aimed to be a wake-up call regarding dyslipidemia, as a disease per-se as well as secondary to other diseases or induced by medication.

MATERIALS AND METHODS

Study design and setting

We conducted two complementary studies at the National Institute for Mother and Child Health "Alessandrescu-Rusescu", Bucharest, Romania. The first was a retrospective, descriptive, cross-sectional study spanning January 2011 – December 2020, analyzing lipid panel results from pediatric patients. The second was a prospective, longitudinal study (2021–2023) focusing on children with suspected familial hypercholesterolemia (FH), including genetic testing and prospective follow-up analysis of patients who returned for re-evaluation after lifestyle and dietary intervention.

Study population and eligibility criteria

The retrospective study included patients aged 0–18 years with at least one complete lipid panel (total cholesterol, HDL-C, LDL-C, triglycerides) performed in our laboratory. We excluded patients with incomplete lipid profiles or missing demographic data.

The prospective study included children (aged under 18 years old) who had LDL-cholesterol value over 130 mg/dL in at least one evaluation in our clinic in the timeframe 2011–2020. Patients with secondary dyslipidemia due to uncontrolled endocrine disorders, nephrotic syndrome, or acute illness were excluded. Patients that already had been genetically tested for FH were also excluded.

Data collection

In the retrospective arm, we analyzed >3000 lipid profiles from 2413 unique patients. Demographic data and clinical diagnoses were extracted from medical records. LDL-C values

>130 mg/dL were considered elevated according to the Romanian Pediatric Guidelines[20].

In the prospective arm, 20 patients underwent genetic testing for FH. Sequencing targeted the LDLR, APOB, and PCSK9 genes. All patients received lifestyle and dietary counseling and were followed for 6–12 months. Lipid parameters were measured at baseline and at follow-up. Only 10 patients completed the prospective study.

Outcomes and variables

For both studies, primary outcomes were prevalence of elevated LDL-C (retrospective) and proportion of patients with pathogenic mutations (prospective). Secondary outcomes included change in LDL-C and total cholesterol after lifestyle intervention, stratified by genetic test results.

Clinical, paraclinical evaluation and genetic testing

Selected patients were evaluated from a clinical and paraclinical point of view. Clinical evaluation included measuring weight, height, and arterial pressure. Paraclinical evaluation included collecting blood vials for evaluation of lipid profile and genetic testing.

Due to financial considerations (extremely high cost of genetic testing) only 20 genetic tests were available. Genetic testing took place at Regional Genetic Testing Center Dolj, Romania.

For each patient, the body-mass-index (BMI) was calculated. For the atherogenic risk we calculated Castelli I, Castelli II Indexes, the Atherogenic Index of Plasma (AIP) and ApoB/ApoA ratio.

At the initial visit the patients received counseling for lifestyle changes and maintaining these changes. Dietetic recommendations were elaborated from several bibliographic sources [21–24]. It was recommended to approach these changes inclusive, as a family, to avoid the child feeling punished. A year after the initial visit the patients were invited for a reevaluation.

For genetic testing TruSigh Cardio enrichment kit was used. The genetic testing was evaluated, optimized, and evaluated at Reginal Medical Genetic Center Dolj. This test evaluated 174 genes associated with 17 cardiac hereditary diseases including FH.

Informed consent and ethics committee approval

For every patient included in this study informed consent was obtained. The study was approved by the ethics committee of the hospital and was conducted in accordance with the Declaration of Helsinki (approval no. 6353/29.05.2019 and no. 12747/16.07.2020).

Statistical analysis

Data were processed and analyzed using Epi Info™ software (Centers for Disease Control and Prevention, Atlanta, USA). Results are presented as absolute numbers and percentages for categorical variables, and as mean ± standard deviation (SD) for continuous variables. Comparisons between groups were performed using the statistical tests available in Epi Info™ (Chi-square or Fisher's exact test for categorical variables; Student's t-test or Mann–Whitney U test for continuous variables, as appropriate). A p-value <0.05 was considered statistically significant.

RESULTS

Retrospective study

For this study more than 3000 lipid panel results were evaluated dating from the timeframe 2011-2020. After eliminating duplicates (multiple evaluations for the same patient) 2413 patients were included. Mean lipid panel results by age groups are presented in Table 1. From the study cohort we identified 440 patients (18,23%) with LDL-cholesterol over 130 mg/dl. The mean age of patients with high LDL-cholesterol is 7,90 years (±4.46). Almost half (47,50%) of them were female. Most of them (69,09%) were from urban areas and 44,77% from Bucharest.

Table 1

Mean lipid panel values by age-groups (n=2413)

	0–2 year (n = 613)	**3–5 year (n = 354)**	**6–8 year (n = 444)**	**9–11 year (n = 455)**	**12–14 year (n = 338)**	**15–18 year (n = 209)**
Total cholesterol (mg/dL)	146,4 (±51,9)	165,9 (±50,5)	167,3 (±44,9)	167,3 (±40,2)	156,9 (±40,1)	154.5 (±39.3)
LDL-cholesterol (mg/dL)	88,2 (±37,1)	107,0 (±43,6)	108,4 (±38,5)	111,0 (±37,2)	102,6 (±36,0)	101.8 (±37.0)
HDL-cholesterol (mg/dL)	41,3 (±15,4)	53,6 (±29,0)	55,5 (±14,1)	53,1 (±14,0)	50,0 (±14,5)	49.1 (±13.6)
Triglyceride (mg/dL)	135,4 (±101,2)	72,6 (±36,9)	81,9 (±55,6)	87,9 (±46,3)	95,5 (±54.7)	86.1 (±49.4)

The mean total cholesterol value for the group with high-LDL-cholesterol was 218,57 mg/dL (±58,46). The highest mean total cholesterol level was recorded in the age group 0–2 years (233,27 mg/dL (±90,51)).

The patients from the high-level LDL-cholesterol group had different diagnosis, the most frequent ones being from the category Endocrine, nutritional and metabolic disease (52,7%). Diagnosis of patients with High LDL-cholesterol are presented in Table 2.

Table 2

Diagnosis of patients with high LDL-cholesterol (over 130 mg/dL)

Diagnostic	**Percentage of patients diagnosed (n=440)**
Endocrine, nutritional**,** and metabolic disease	52,75%
• Overweight, obesity and other hyperalimentation	25,91%
• Metabolic disorders (including familial hypercholesterolemia)	11,37%
• Malnutrition	11,14%
• Disorders of the thyroid gland (hypothyroidism)	4,10%
• Diabet**es** mellitus	0,23%
Other	28,65%
Diseases of the respiratory system	3,41%
Mental, Behavioral and Neurodevelopmental disorders	3,21%
Diseases of the digestive system	2,96%
Diseases of the nervous system	2,51%
Congenital malformations, deformations, and chromosomal abnormalities	2,29%
Disease of the musculoskeletal system and connective tissue	1,59%
Diseases of the genitourinary system	0,92%
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	0,69%
Diseases of the eye and adnexa	0,68%
Diseases of the circulatory system	0,23%
Neoplasms	0,23%

More than 10% of the patients with high LDL-cholesterol values were diagnosed with metabolic disorders, including dyslipidemia (40 patients). 3,21% of high-LDL-cholesterol patients were diagnosed with neuropsychiatric disorders and conduct disorders while 2,51% were diagnosed with neurologic disorders.

Our clinic offers genetic counseling, therefore having high addressability for patients with genetic disease. 2,29% of patients with high LDL-cholesterol had congenital malformations or chromosomal abnormalities such as Down Syndrome or Prader-Willi Syndrome.

Table 3 presents lipid panel mean values by pathology in the high-LDL-cholesterol group.

Table 3

Lipid panel mean values by pathology

Diagnostic	Total cholesterol (mg/dL)	LDL-cholesterol (mg/dL)	HDL-cholesterol (mg/dL)	Triglyceride (mg/dL)
Endocrine, nutritional, and metabolic diseases	216,19 (± 48,12)	161,84 (± 41,26)	51,73 (± 15,08)	110,26 (± 63,50)
Other	216,70 (± 66,24)	155,19 (± 30,01)	57,20 (±42,74)	100,35 (± 59,51)
Diseases of the respiratory system	206,53 (± 38,47)	151,33 (± 21,00)	50,71 (± 21,11)	128,28 (± 64,90)
Mental, behavioral, and neurodevelopmental disorders	229,46 (± 46,19)	176,35 (± 38,81)	53,78 (± 12,39)	101,35 (± 58,02)
Diseases of the digestive system	224,08 (± 62,36)	166,84 (± 47,57)	52,30 (± 20,23)	80,23 (± 65,10)
Diseases of the nervous system	222,40 (± 38,12)	151,90 (± 25,06)	49,00 (± 14,14)	135,70 (± 69,84)
Congenital malformations, deformations, and chromosomal abnormalities	207,75 (± 49,52)	158,90 (± 35,50)	41,30 (± 16,85)	123,77 (± 76,08)
Diseases of the musculoskeletal system and connective tissue	211,85 (± 56,63)	158,85 (± 42,27)	50,00 (± 16,75)	75,14 (± 20,31)
Diseases of the genitourinary system	432,00 (± 114,89)	325,00 (± 111,24)	57,75 (± 6,80)	253,75 (± 287.98)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	236,00 (± 22,06)	183,66 (± 39,39)	42,00 (± 2,64)	147,33 (± 38,00)
Diseases of the eye and adnexa	205,66 (± 33,82)	172,00 (± 24,87)	48,00 (± 6,00)	99,00 (± 24,02)
Diseases of the circulatory system	200,00 (NA*)	138,70 (NA*)	60,00 (NA*)	91,00 (NA*)
Neoplasms	205,00 (NA*)	148,00 (NA*)	52,00 (NA*)	185,00 (NA*)

Prospective study

In this study 20 patients were genetically tested for familial hypercholesterolemia.

In 8/20 cases (40%) we identified a agentic variant implicated in the etiopatogenic diagnosis for FH: 4 patientd had mutation on LDLR gene (type 1 FH), 2 patients in PCSK9 gene (type 3 FH) and 2 patients had APOB gene mutations (type 2 FH). The mutations identified are presented in Table 4.

The study group was divided in two: group A – negative genetic testing for FH (12 patients) and group B – positive genetic testing for FH (8 patients).

The average age of patients included in the prospective study was 9,70 years (±4,09). The mean age in the positive genetic testing group was 9,00 years (±6,26) while in the negative genetic-testing group the mean age was 10,16 years (±4,58). Ten patients were female, 3 of them in the positive genetic testing group.

During clinical examination, no clinical signs or symptoms suggesting FH were found in any of the patients evaluated.

Family history revealed cardiovascular events at young ages in Ist and IInd degree relatives in 10 out of 20 patients. Unexpectedly, 7 of them were in the negative genetic testing group.

Only 16,67% (3/20) of patients had normal weight for age and gender. 38,89% (7/20) patients included in the study were underweight while 22,22% (4/20) had class I obesity.

Ten patients came for a reevaluation, 4 from the genetic negative group and 6 from the genetic positive group. In the genetic negative group, after initiation of dietary and lifestyle changes and maintaining for 1 year, the total cholesterol level decreased by 13,34% while for the patients with positive genetic testing the decrease was of only 7,93%. In the genetic negative group, after initiation of hygieno-dietetic treatment, LDL-cholesterol decreased by 18,5% while for the patients with positive genetic testing the decrease

of LDL-cholesterol was insignificant (mean LDL-cholesterol values decreased by 0,63%).

The changes observed in lipid panel values for the two genetic groups are illustrated in Figs. 1, 2.

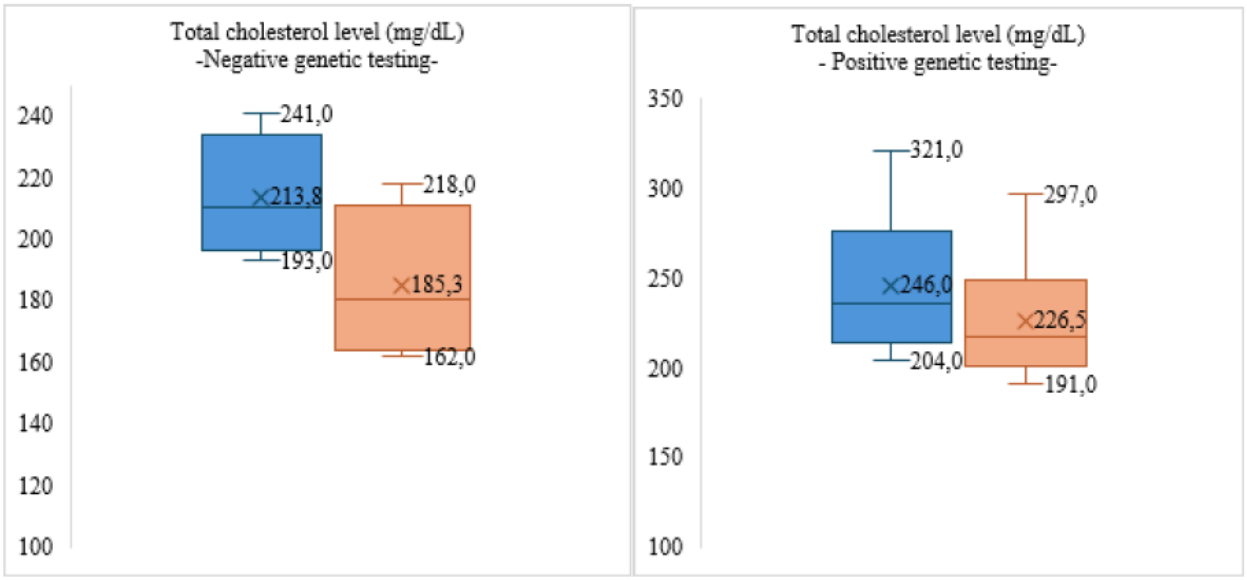

Fig. 1 – Total cholesterol mean values in the genetic positive (image on the right side) and genetic negative groups (image on the left side) at initial evaluation (blue) and reevaluation (orange).

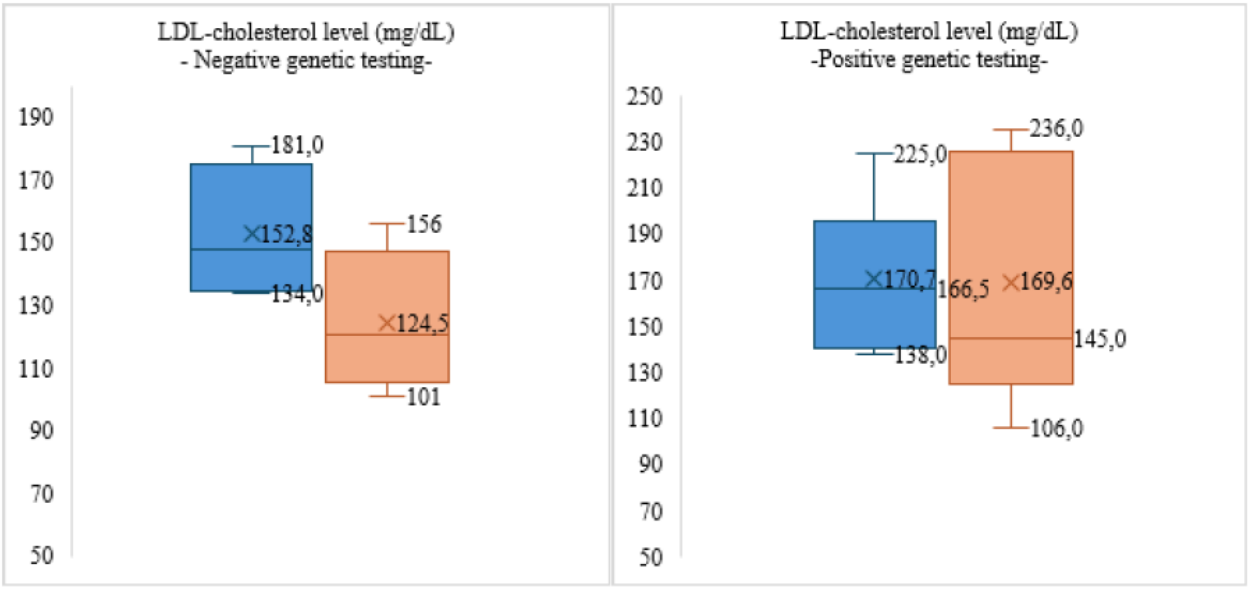

Fig. 2 – LDL-cholesterol mean values in the genetic positive (image on the right side) and genetic negative groups (image on the left side) at initial evaluation (blue) and reevaluation (orange).

DISCUSSION

Prevalence of lipid panel abnormalities in pediatric population is estimated at 8–20%[25]. In our study, 18,23% of the patients had high LDL-cholesterol (≥130 mg/dL), a high percentage when compared with the prevalence of dyslipidemia in pediatric patients reported by other studies.

In our study, 31,82% of the patients aged between 0 and 9 years had high TG levels (≥100 mg/dL), and 21,6% of the ones aged between 0 and 2 years. We can safely assume that most of the children aged 0-2 years are breastfed or receive some kind of milk formula. In this age group, the TG plasmatic levels is often high (up to 150–200 mg/dL)[26–28]. This high value could be explained by

the feeding particularities and timing. Infants are fed at short intervals and the probability for the blood test to have been drawn in a fasting state is low.

More than a quarter of the patients (25,91%) were diagnosed with obesity. In another recent study, that took part in the west part of Romania[29], the prevalence of overweight and obese children was estimated under 30%.

In this study 4,1% of the patients with high LDL-cholesterol were diagnosed with congenital hypothyroidism. In other studies, among patients with hypothyroidism, 30% had high total cholesterol and LDL-cholesterol while 90% had dyslipidemia[30,31].

Results from this study were published in the Journal Medicina with the title *Dyslipidemia in Pediatric Patients: A Cross-Sectional Study*[32].

FH is characterized by high LDL-cholesterol since birth, which, in time, leads to an increased risk for atherosclerotic cardiovascular disease. Despite all information accumulated about FH it remains underdiagnosed and undertreated, being marked by high mortality and morbidity due to atherosclerotic cardiovascular disease[33].

From a clinical point of view and looking at the lipid profile of patients with positive and negative genetic testing for FH the differences were not statistically significant. However, there has been a higher decrease of LDL-cholesterol levels after dietary and lifestyle measures in patients with negative genetic testing, therefore a better outcome. This suggests the need to identify the patients that have genetic mutations corelated with FH and taking into consideration initiating medication for selected cases.

This study is among the first ones in Romania that aims to contribute to the early diagnosis of FH and reduce significantly the morbidity and mortality that these patients have because of atherosclerotic cardiovascular disease. In this study Next Generation Sequencing (NGS) was used to identify genetic mutations in patients with clinical clues for FH. As far as we know there is no other Romanian study describing genetic mutations associated with FH in pediatric patients.

In this study the detection rate was 40%, 8 patients with mutations identified, 5 with pathogenic/probable pathogenic mutations and 3 with variants of uncertain significance. The pathogenic/probable pathogenic variants were mostly on LDLR gene. In this study 2 patients had APOB mutations, one classified as VUS and one probable pathogenic. In this study there were no new mutations identified, all the mutations being described before.

The lack of genetic studies for FH in our country does not allow us to correlate the results geographically. We consider that additional studies are required, including more patients, extending on a larger area, in order to identify mutation responsible for FH phenotype in Romania.

This study has certain limitations. The number of patients included is very small due to the high costs of genetic testing. Also, this study was conducted in a single center and can not be generalized for the country or region.

Results from this study were published partially in the journal Diagnostics, with the title *Genetic Testing for Familial Hypercholesterolemia in a Pediatric Group: A Romanian Showcase* [34] and partially in Medicina, with the title: *The Importance of Genetic Testing for Familial Hypercholesterolemia: A Pediatric Pilot Study*[35].

CONCLUSION

This retrospective descriptive study supports through its results the utility and necessity for implementing a national screening program. Such a measure could reduce the cardiovascular disease burden at young ages (before 50 years) that falls on the patient because it affects his quality of life and reduces his work capacity as well as on the health system through the costs these potentially severe pathologies generate.

In our country there is no national screening program for dyslipidemia in pediatric patients. Taking this into consideration, primary dyslipidemia is underdiagnosed.

Results from this study support the working hypothesis and the expected results were confirmed, towards the objectives set.

In this study 8 out of 20 patients were genetically tested positive for FH. Most of them were on LDLR gene but there were also mutations in APOB and PCSK9 genes. Several variants have been reported in other studies (LDLR c.1618G>A, LDLR c.1775G>A).

Evaluating the lipid profile is the first step towards clinical diagnosis for FH and it is universally available, at low costs. Genetic testing remains, however the gold standard for FH diagnosis[36].

Additional studies, on larger patient groups are needed, aiming the genetic spectrum of FH in

Romania, and to identify indexes appropriated for evaluating atherosclerotic risk in these patients.

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