

Refinement of the diagnostic approach for the identification of children and adolescents affected by familial hypercholesterolemia: Evidence from the LIPIGEN study

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ABSTRACT

Background and aims: We aimed to describe the limitations of familial hypercholesterolemia (FH) diagnosis in childhood based on the presence of the typical features of FH, such as physical signs of cholesterol accumulation and personal or family history of premature cardiovascular disease or hypercholesterolemia, comparing their prevalence in the adult and paediatric FH population, and to illustrate how additional information can lead to a more effective diagnosis of FH at a younger age.

Methods: From the Italian LIPIGEN cohort, we selected 1188 (≥ 18 years) and 708 (< 18 years) genetically-confirmed heterozygous FH, with no missing personal FH features. The prevalence of personal and familial FH features was compared between the two groups. For a sub-group of the paediatric cohort ($N = 374$), data about premature coronary heart disease (CHD) in second-degree family members were also included in the evaluation.

Results: The lower prevalence of typical FH features in children/adolescents vs adults was confirmed: the prevalence of tendon xanthoma was 2.1% vs 13.1%, and arcus cornealis was present in 1.6% vs 11.2% of the cohorts, respectively. No children presented clinical history of premature CHD or cerebral/peripheral vascular disease compared to 8.8% and 5.6% of adults, respectively. The prevalence of premature CHD in first-degree relatives was significantly higher in adults compared to children/adolescents (38.9% vs 19.7%). In the sub-cohort analysis, a premature CHD event in parents was reported in 63 out of 374 subjects (16.8%), but the percentage increased to 54.0% extending the evaluation also to second-degree relatives.

Conclusions: In children, the typical FH features are clearly less informative than in adults. A more thorough data collection, adding information about second-degree relatives, could improve the diagnosis of FH at younger age.

1. Introduction

Familial hypercholesterolemia (FH) is the most common inherited metabolic disease with an autosomal dominant mode of inheritance, characterized by high levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) since birth, leading to premature coronary artery disease (CAD) [1].

Owing to a genetic defect mainly in the low-density lipoprotein (LDL)-receptor (LDLR) pathway, affected patients cannot clear LDL particles from the circulation, causing a life-long accumulation of low-density lipoprotein cholesterol (LDL-C) in plasma and a consequent accelerated atherosclerosis process, if untreated [2].

Although the high cardiovascular risk associated with the disease makes early diagnosis and initiation of treatment of outmost

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importance, identifying individuals with FH at a younger age poses several challenges [3,4]. In most international contexts, as in Italy, there is no systematic paediatric screening, and the diagnosis of FH in children and adolescents is mostly by chance or after cascade screening following the identification of an affected person in the family. Moreover, it is often entrusted to non-specialised physicians, mostly paediatricians, with fragmentary or limited knowledge about FH.

The utilisation of algorithms supporting the clinical diagnosis, such as the Dutch Lipid Clinic Network (DLCN) score [5] recommended by European guidelines [6] or Simon Broome (SB) criteria [7], is of limited applicability in children [8,9]. These tools are essentially based on clinical features of the disease in adulthood, which are often absent in subjects under 18 years: high LDL-C levels and their consequences, i.e. physical signs of lipid accumulation (xanthomas, xanthelasmas, and juvenile corneal arch) and the onset of premature cardiovascular events (before 55 years in men and before 60 years in women), as well as a family history of hypercholesterolaemia and early cardiovascular events [4,10–12]. Indeed, with the exception of the most severe cases of FH in homozygous form, LDL-C levels in FH children and adolescents are often not as high as in adults, and could be influenced by puberty [13,14]. In addition, the cumulative cholesterol burden is usually not sufficient to result in the development of physical signs or early events. Finally, the young age of the children often coincides with the young age of the parents, who often do not have (yet) developed a cardiovascular event despite the presence of FH, also thanks to treatment with lipid lowering medications [4,15]. Moreover, as also reported in adult age [16], the applicability of the diagnostic algorithms can be limited by the difficulties to retrieve all crucial parameters/information, such as diseases and health conditions in the family.

These limitations call for further research in the population of young patients with FH. A valuable support is offered by disease registries, which collect relevant clinical, biochemical, and genetic information [17]. In Italy, the LIPIGEN register has been active since 2016, thanks to the collaboration of more than 50 lipid clinics throughout the country [18], committed to collecting data on patients with a clinical or genetic diagnosis of FH. Within the main project, the LIPIGEN Paediatric Group was created in 2018 [13]. One of the aims of this initiative was to refine data collection in the sub-population of young FH patients, in order to provide the basis for an improved diagnostic and therapeutic approach.

The aim of the present analysis was to describe the limitations of relying on the presence of typical features of FH for a diagnosis in paediatric subjects, and to illustrate how the integration of data collection with additional information can support the diagnosis of FH at a younger age.

2. Patients and methods

2.1. Study population and data source

The LIPIGEN-FH study is an observational, multicentre, retrospective and prospective study [18]. The study has been approved by the Institutional Review Board of each participating center and conducted in accordance with the principles of the Helsinki Declaration, the standards of Good Clinical Practice (ICH GCP), the data protection laws, and other applicable regulations. Patients of any age and sex, with clinical suspicion of FH, who are able to understand the study procedures and who voluntarily agree to participate by providing written informed consent, may be included in the study. Detailed information about the procedures of LIPIGEN study has been previously published [18].

We restricted our analysis to adults (≥ 18 years) and children/adolescents (< 18 years), with genetic diagnosis of heterozygous FH (i.e., with one causative variants in one of the FH-causing candidate genes [19]), without missing values in personal criteria [5] such as data about physical examination and personal clinical history, and with known untreated LDL-C levels.

2.2. Patient characteristics

For each subject, anamnestic, anthropometric, biochemical and genetic data were collected.

The prevalence of several FH features was evaluated for both cohorts. Typical clinical manifestations of FH included (in addition to LDL-C) personal clinical history of tendon xanthoma or arcus cornealis at age before 45 years at physical examination, development of a premature coronary heart disease and/or premature cerebral or peripheral vascular disease in the subjects (before 55 years in males and before 60 years in females). Data about family history considered the presence of first-degree relative with known premature coronary heart disease (CHD), with hypercholesterolemia (LDL-C > 190 mg/dL), and/or with tendon xanthoma/cornealis arcus at age < 45 .

The work of the LIPIGEN Paediatric Group led to the integration of the electronic Case Report Form (eCRF), initially designed only for adult patients, with additional information specifically for children and adolescents. Based on the observation that children with FH have parents who are often young and already under lipid-lowering treatment, two factors that reduce the likelihood of a premature cardiovascular event, the family cardiovascular history evaluation was extended to grandparents.

Table 1

Prevalence of typical features of FH in adults (N = 1188) and in subjects under 18 years (N = 708).

	Adults	Subjects < 18 y	p
Females, %	52.8	50.6	0.37
Age in years, mean SD	40.7 \pm 14.6	10.3 \pm 4.2	
Untreated LDL-C (mg/dL), mean SD	269.1 \pm 71.3	227.5 \pm 50.4	< 0.0001
LDL-C > 155 mg/dL, %	98.1	94.2	< 0.0001
LDL-C > 190 mg/dL, %	91.8	76.4	< 0.0001
LDL-C > 250 mg/dL, %	55.7	28.4	< 0.0001
Physical examination, %			
Tendon xanthoma	13.1	2.1	< 0.0001
Arcus cornealis at age < 45	11.2	1.6	< 0.0001
Clinical history, %			
Clinical history of premature CHD	8.8	0.0	< 0.0001
Clinical history of premature cerebral or peripheral vascular disease	5.6	0.0	< 0.0001
Family history, %			
First-degree relative with known premature CHD	38.9	19.7	< 0.0001
First-degree relative with known LDL-C > 190 mg/dL	92.9	93.5	0.63
First-degree relative with tendon xanthoma and/or corneal arcus at age < 45	18.7	20.0	0.52

LDL-C LDL-cholesterol; CHD coronary heart disease.

2.3. Statistical analysis

Continuous variables are expressed as mean and standard deviation (SD) while categorical data as absolute frequencies and percentages. Continuous variables were compared using *t*-test, while categorical variables were compared by chi-square or Fisher's exact tests.

Data analysis was performed using SAS (Statistical Analysis System) software version 9.4 (SAS. Institute, Inc. Cary, North Carolina), and two-tailed $p < 0.05$ was considered for statistical significance in all analyses.

3. Results

A total of 1896 genetically confirmed heterozygous FH subjects (N = 1188 adults [52.8% females], and N = 708 children/adolescents [50.6% females]) were included in the analysis (Table 1), with a mean age of 40.7 ± 14.6 years and 10.3 ± 4.2 years, respectively. The prevalence of the typical features of FH was lower in children/adolescents compared to adults: tendon xanthoma was identified in 13.1% of adult vs 2.1% of children/adolescent patients ($p < 0.0001$), a similar difference was detected also for the arcus cornealis (11.2% vs 1.6%, $p < 0.0001$, respectively). No children presented a clinical history of premature CHD or cerebral/peripheral vascular disease, identified in 8.8% and 5.6% of the adults, respectively.

The prevalence of first-degree relatives with tendon xanthoma and/or corneal arcus was comparable among adults and children (18.7% and 20.0%, respectively; $p = 0.52$), as well as the presence of hypercholesterolemia in first-degree family members (92.9% vs 93.5%, respectively; $p = 0.63$). A premature CHD in first-degree relatives was reported in 38.9% of adult FH, and only in 19.7% of subjects under 18 years ($p < 0.0001$). Adults also presented significantly higher level of untreated LDL-C compared to the paediatric cohort: 269.1 ± 71.3 mg/dL vs 227.5 ± 50.4 ($p < 0.0001$; Fig. 1); in addition, the percentage of subjects with LDL-C values above 250 mg/dL in adults was two times higher than children/adolescents (55.7% vs 28.4%, $p < 0.0001$).

The analysis on additional data collection in the paediatric population about premature event also in second-degree relatives was carried out on a subgroup of 374 children/adolescents for whom this information was available. This sub-cohort was representative of the whole paediatric cohort, as no significant differences in sex, age at baseline, untreated LDL-C levels, and clinical manifestation of FH were observed (data not shown).

A premature cardiovascular event in the parents was reported in 16.8% of the paediatric sub-group, but the percentage increased to 54.0% extending the evaluation also in second-degree family members

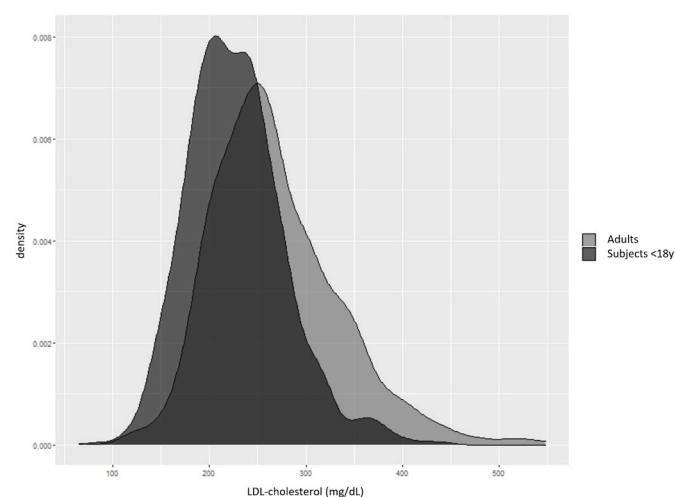


Fig. 1. Distribution of LDL-cholesterol (mg/dL) among adults and subjects <18 years.

(Fig. 2). In details, 136 subjects presented a premature CHD at least in one grand-parent and 19 subjects at least in one parent and/or one grand-parent. Within the paediatric sub-group with LDL-C >190 mg/dL (74.1%), the prevalence increased from 14.8% to 54.2%.

4. Discussion

Our analysis clearly illustrated that the criteria routinely used for the clinical diagnosis of FH in adults are less effective at detecting paediatric patients. The comparison between the phenotype of LIPIGEN adults and children allowed to identify a significant higher prevalence of typical features of FH in adults which were less frequent in children. This difference can be explained by their young age and temporal limited exposure to high levels of LDL-C (less cumulative cholesterol burden) leading to the lack of typical signs of FH, as reported also in a Portuguese FH cohort, where out of 295 children (mean age 10 years old) none presented with CHD or tendon xanthoma [20].

The first obvious adjustment for a better clinical decision making relates to the cut-offs for LDL-C. However, this cannot simply be solved by reducing the thresholds, as fluctuations in cholesterol concentrations with age are present [13], and the approach should be age-specific. As such, a diagnostic approach based primarily on LDL-C would lead to the identification of only the most severe cases, with very high levels, and would be poorly sensitive. Therefore, the evaluation of the family history becomes relevant, even more so in the younger population.

In our analysis, we investigated whether additional parameters can improve the FH diagnosis in children [21], by further leveraging on family history. Our data show a significant difference in the prevalence of first-degree relatives with known premature CHD, only in 21% of children compared to 39% of adults. Notably, once we extended the family history information to second-degree family members in the paediatric sub-cohort, the prevalence of premature CHD in first- and second-degree relatives increased to more than 54% (Fig. 3). A similar trend was also observed in the Dutch registry where a history of CHD was reported in 20% of FH parents (mean age 41 years old) and in 49% of grand-parents (mean age 51 years) [22].

These observations support the proposal of refinements of the diagnostic approach with a tailored data collection at younger age and emphasises the importance of assessing, in all children visiting a doctor (whatever the reason), the family history regarding cholesterol levels, cardiovascular disease and confirmed or suspected genetic conditions not only in parents, but also extending the evaluation at least at second-degree family members.

In a disease such as FH, early diagnosis remains a central point to control for the exceedingly high risk of this population, if untreated. Many screening approaches have been proposed, targeting different age groups, and none has proved better than the others [23]. The simple lipid test, combined with an accurate family history evaluation, may be a viable and low-cost option.

On the other hand, it should be noted that the main limitation of this approach is related to the difficulties in collecting family data. In particular cases, such as adoptions, complex family situations, or others, to reconstruct family data is challenging [4]. The inclusion criteria for this analysis were established to reduce the relevant impact of missing data on the performance of diagnostic algorithms, as previously demonstrated [16]. However, an evaluation on the whole LIPIGEN cohort showed that information about family history resulted to be difficult to be gather in both age groups (in the overall LIPIGEN cohort, proportions of missing data about premature CHD in first-degree family members: 4.7% in adults and 4.9% in children/adolescents; proportions of missing data about presence of LDL-C >190 mg/dL in first-degree family members: 7.8% in adults and 10.2% in children/adolescents; data not shown). To improve FH detection and to fill in this gap, general practitioners and family paediatricians should be aware of the importance of collecting a CHD-oriented family history. Moreover, any medical doctor who takes care of adult or paediatric subjects should

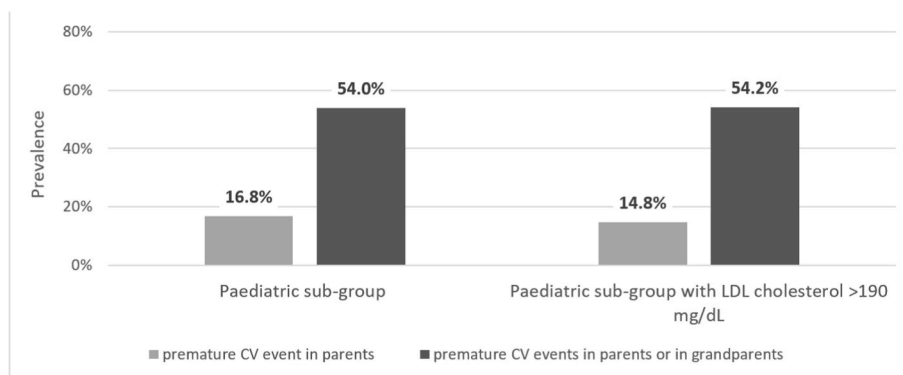


Fig. 2. Prevalence of premature cardiovascular (CV) events in parents/grandparents reported in the whole paediatric subgroup and in children/adolescent with LDL-cholesterol >190 mg/dL.

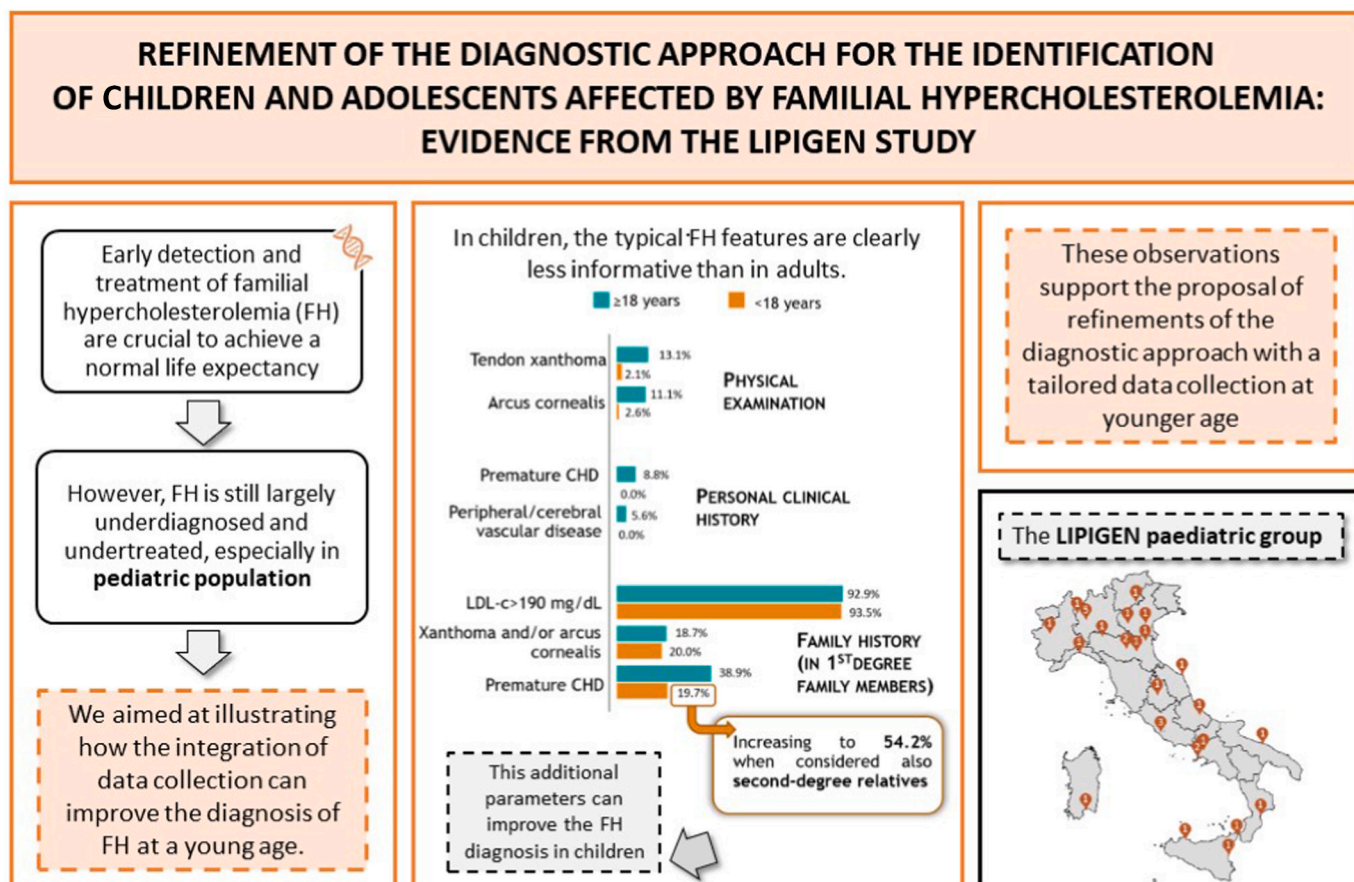


Fig. 3. Graphical abstract.

periodically update CHD-oriented family history data.

The high number of paediatric patients in the LIPIGEN register is one of the main strengths of our network, as well as the presence in the same national register of both adult and paediatric populations. However, our results should be interpreted considering potential limitations. One criticism relates to the absence of control cohorts of non-FH patients, which will be crucial for future evaluation of the specificity of an adapted diagnostic algorithm [24]. On the other hand, in order to have robust results, we limited our cohort to subjects with genetic diagnosis of FH. However, it was shown that, in a considerable proportion of subjects with a FH phenotype, no pathogenic variant is found [25]. Genetically negative subjects show mostly a milder phenotype [26], and in these subjects the described limitations for early diagnosis would be even

more impactful.

In conclusion, the analysis of data extracted from the LIPIGEN registry highlighted few challenges in FH diagnosis, especially for paediatric patients. Clearly, FH diagnosis based on signs of the disease and on the clinical consequences of medium-to long-term exposure to high LDL-C levels is not efficient in young patients. Our evidence should discourage the stringent use of diagnostic algorithms in this population. On the other hand, the hallmark of the disease is primarily the elevated lipid levels. This implies the need to measure these levels in the paediatric population. This assessment would provide the starting point for a diagnostic suspicion, which can be supported by family investigation, extended to second-degree relatives when the information is available. Health decision-makers could consider targeted paediatric screening,

perhaps by integrating cholesterol measurement with the administration of childhood vaccines, or by providing free screening in primary schools. Another strategy that needs to be enhanced is the cascade screening, i.e. screening in the children of adults affected by FH. Finally, it is important to highlight that once a child is diagnosed with FH as index case in a family, this should lead to screening in all family members (the so-called reverse cascade screening). We believe that active collaboration among medical doctors dealing with adult subjects and with paediatric ones, together with institutions' and patients associations' involvement, will help spread FH knowledge and awareness, and increase the number of patients diagnosed with FH since childhood [27].

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Data availability statement

The data that support the findings of this study are available from the corresponding author (MC) upon reasonable request.

CRediT authorship contribution statement

Manuela Casula: Investigation, Data curation, Writing – original draft. **Marta Gazzotti:** Investigation, Data curation, Writing – original draft. **Maria Elena Capra:** Conceptualization, Methodology, Writing – review & editing. **Elena Olmastroni:** Formal analysis. **Federica Galimberti:** Writing – original draft. **Alberico L. Catapano:** Conceptualization, Supervision, Writing – review & editing. **Cristina Pederiva:** Conceptualization, Methodology, Writing – review & editing.

Declaration of competing interest

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