Familial Hypercholesterolemia: A Narrative Review on Diagnosis and Management Strategies for Children and Adolescents

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Abstract: Familial hypercholesterolemia (FH) is a relatively common inherited disorder caused by deleterious mutation(s) in the low-density lipoprotein (LDL) receptor or its associated genes. Given its nature as a heritable disease, any useful screening scheme, including universal, and cascade screening, allows for the early identification of patients with FH. Another important aspect to note is that early diagnosis associated with appropriate treatment can promote better prognosis. However, most clinical diagnostic criteria for adults have adopted clinical elements, such as physical xanthomas and family history, both of which are usually obscure and/or difficult to obtain in children and adolescents. Moreover, LDL cholesterol levels fluctuating considerably during adolescence, hindering the timely diagnosis of FH. In addition, recent advancements in human genetics have revealed several types of FH, including conventional monogenic FH, polygenic FH caused by common single nucleotide variations (SNV) accumulation associated with elevated LDL cholesterol, and oligogenic FH with multiple deleterious genetic variations leading to substantially elevated LDL cholesterol. The aforementioned findings collectively suggest the need for amassing information related to genetics and imaging, in addition to classical clinical elements, for the accurate diagnosis of FH in this era of personalized medicine. The current narrative review summarizes the current status of the clinical and genetic diagnosis of FH in children and adolescents, as well as provide useful management strategies for FH in children and adolescents based on currently available clinical evidence.

Keywords: familial hypercholesterolemia, cardiovascular disease, statin, children, adolescents

Introduction
Low-density lipoprotein (LDL) cholesterol has been identified as the causative factor for atherosclerotic cardiovascular disease (ASCVD) based on a variety of evidence obtained from epidemiology, human pathophysiology, human genetics, and clinical trials. Familial hypercholesterolemia (FH), an inherited hyper-LDL cholesterol, has often been associated with tendon and cutaneous xanthomas and premature ASCVD. This disorder has been regarded as a Mendelian autosomal dominant disease caused by rare genetic mutation(s) in the LDL receptor or its associated genes. Theoretically, this disease can be diagnosed at the early stages of life, even as early as pregnancy. Currently, two major methods have been proposed for the screening of FH worldwide. The first approach involves cascade screening where a diagnosis of FH in new cases, typically younger relatives, is triggered by...
the diagnosis of the index cases. The second approach involves universal screening where LDL cholesterol measurements are conducted universally at a certain age, after which detailed assessments, including genetic analyses, are subsequently performed to confirm their diagnoses. However, diagnosing FH in children and adolescents is often quite difficult given that physical xanthomas and family histories are usually obscure and/or difficult to obtain among such young patients.

Apart from the difficulties in diagnosing FH among children and adolescents, debates regarding when, how, and who to treat at this early stage of life have remained ongoing. In this regard, recent advancements in human genetics have revealed that personalized medicine can also be applicable to FH, where patients with deleterious genetic mutations and/or signs of premature atherosclerosis development should be treated earlier and more aggressively. On the other hand, children and adolescents with FH who had started early treatment exhibited excellent prognosis even under mild treatment, suggesting the importance of earlier treatment in the management of FH.

The current review outlines the current status of clinical and genetic diagnosis of FH in children and adolescents while also providing useful management strategies for FH in children and adolescents based on currently available clinical evidence.

Familial Hypercholesterolemia and Its Importance

FH is characterized by the clinical triad of primary hyper-LDL cholesterolemia, tendon xanthomas, and premature ASCVD. The first documentation of FH dates back as far as 1873, during which it had been described as xanthomatous disease. By the 1930s, FH had started to be considered as an inherited disease, with Prof. Brown and Goldstein later discovering genetic abnormalities in the LDL receptor as the principal cause of this condition by the 1970s. Subsequently, other genes, including apolipoprotein B (APOB) and proprotein convertase subtilisin/kexin type 9 (PCSK9) genes, have also been identified to cause this disease. Since its initial documentation, FH has long been described to have a prevalence of 1 in 500 individuals among the general population. In 2011, our group found that FH had a prevalence of 1 in 208 based on genetic epidemiology of homozygous FH in the Hokuriku district of Japan. Following our report, similar estimates have been obtained in the United States and Europe. Currently, FH is considered to have a prevalence of 1 in ~300 individuals among the general population. By such estimates, only one monogenic mutation causes the critical phenotype. Monogenic FH is considered the “standard” form of FH, wherein the mutation status of affected genes is associated with increased likelihood of developing ASCVD, independent of LDL cholesterol values. This disease appears to account for at least a portion of patients with ASCVD (estimated to be ~1 in 31 individuals), especially those with premature ASCVD (estimated to be ~1 in 15 individuals). No other single disorder can be responsible for such proportions of ASCVD, which has been identified as the leading cause of mortality worldwide. Moreover, timely diagnosis and treatment of children and adolescents with FH have been shown to promote a favorable prognosis. Accordingly, children and adolescents with require better awareness and more attempts at diagnosing FH compared to adults.

Screening for Familial Hypercholesterolemia: Universal Screening, Opportunistic Screening, Cascade Screening, and Reverse Cascade Screening

As stated previously, timely diagnosis and treatment has been shown to prevent ASCVD events in patients with FH. As such, identifying patients with FH at a younger age is of particular importance given that this leads to prompt treatment initiation and prevention of premature ASCVD. However, diagnosing FH in younger individuals is somewhat difficult considering that they typically do not exhibit increased Achilles tendon thickness, which has been used as one of the major diagnostic criteria for adult FH worldwide. One proposed screening method for FH is universal screening at an age when FH can be effectively identified. 24,25 On the other hand, opportunistic screening, utilizing every opportunity to screen patients for FH, is also effective to find FH.26-28 For example, measurement of LDL cholesterol is common practice, and we can find patients with FH when LDL cholesterol level is over a threshold irrespective of the primary aim of its measurements. Another effective screening method for FH is cascade screening, which has been recommended by many organizations around the world. Indeed, countries where dedicated cascade screening programs have been implemented have identified a notably higher number of patients...
Clinical Diagnosis of Familial Hypercholesterolemia in Children and Adolescents

Several different types of clinical diagnostic criteria have been established for FH globally, including the Dutch Lipid Clinical Network (DLCN),35 Make Early Diagnosis to Prevent Early Deaths (MEDPED) diagnostic criteria,36 Japan Atherosclerosis Society (JAS) FH diagnostic criteria,37 and Simon Broome diagnostic criteria for FH.35 Each of the aforementioned diagnostic criteria for pediatric FH has specific cutoffs for LDL cholesterol (Boxes 1 and 2; Tables 1 and 2) given the considerable variability in its levels within this group, especially among adolescents.38 Moreover, children and adolescents with FH barely exhibit physical xanthomas, which is one of the major clinical diagnostic criteria for adults. Nonetheless, care should be exercised when using lower LDL cholesterol thresholds for screening young patients with FH, with family history being much more important in pediatric than in adult cases. In this regard, clinical diagnostic criteria for pediatric FH by JAS appears to be quite useful. Because it is quite simple to use (there are only 2 elements), and it really put weight on their family history (of parents). In order to diagnose them as FH, (reverse)
Table 1 Diagnosis of Familial Hypercholesterolemia (MEDPED)

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>First Degree Relative with FH</th>
<th>Second Degree Relative with FH</th>
<th>Third Degree Relative with FH</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>220 (5.7)</td>
<td>230 (5.9)</td>
<td>240 (6.2)</td>
<td>270 (7.0)</td>
</tr>
<tr>
<td>20–29</td>
<td>240 (6.2)</td>
<td>250 (6.5)</td>
<td>260 (6.7)</td>
<td>290 (7.5)</td>
</tr>
<tr>
<td>30–39</td>
<td>270 (7.0)</td>
<td>280 (7.2)</td>
<td>290 (7.5)</td>
<td>340 (8.8)</td>
</tr>
<tr>
<td>≥40</td>
<td>290 (7.5)</td>
<td>300 (7.8)</td>
<td>310 (8.0)</td>
<td>360 (9.3)</td>
</tr>
</tbody>
</table>

Note: FH is diagnosed when total cholesterol exceeds these cutoff points in mg/dL (mmol/L).

Abbreviations: MEDPED, Make Early Diagnosis to Prevent Early Deaths; FH, familial hypercholesterolemia.

Table 2 Simon Broome Diagnostic Criteria for FH

<table>
<thead>
<tr>
<th>Point</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Total cholesterol levels &gt; 290 mg/dL (7.5 mmol/L) or LDL-C &gt; 190 mg/dL (4.9 mmol/L) in adults.</td>
</tr>
<tr>
<td></td>
<td>Total cholesterol levels &gt; 260 mg/dL (6.7 mmol/L) or LDL-C &gt; 155 mg/dL (4.0 mmol/L)</td>
</tr>
<tr>
<td>2</td>
<td>Tendon xanthomas in the patient or tendon xanthomas in a first or second degree relative.</td>
</tr>
<tr>
<td>3</td>
<td>DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.</td>
</tr>
<tr>
<td>4</td>
<td>Family history of myocardial infarction before age 50 years in a second degree relative or before age 60 years in a first degree relative.</td>
</tr>
<tr>
<td>5</td>
<td>Family history of elevated total cholesterol &gt; 290 mg/dL (7.5 mmol/L) in an adult first or second-degree relative.</td>
</tr>
<tr>
<td></td>
<td>Family history of elevated total cholesterol &gt; 260 mg/dL (6.7 mmol/L) in a child, brother, or sister 16 years or younger.</td>
</tr>
</tbody>
</table>

Diagnosis

Definite FH = 1+2 or 3
Possible FH = 1+4 or 5

Abbreviations: LDL-C, low-density lipoprotein cholesterol; FH, familial hypercholesterolemia; PCSK9, proprotein convertase subtilisin/kexin type 9.

should be carefully considered. However, we also need to be careful for what is FH. A few years ago, an useful classification has been proposed regarding the classification of FH. According to this, FH can be classified into heterozygous FH (caused by a deleterious mutation in FH-gene), homozygous FH (caused by double deleterious mutations in FH-gene), polygenic FH (caused by LDL-associated common genetic variations), and polygenic FH plus hypertriglyceridemia (caused by LDL-, and TG-associated common genetic variations). In terms of genetic diagnosis, it is still quite difficult to diagnose polygenic state of FH. Accordingly, genetic diagnosis of FH is usually referring to genetic testing for rare genetic variations of FH-genes. In addition, it is also important to think differently between heterozygous FH and homozygous FH irrespective of ages. As stated above, the prevalence of “heterozygous” FH is 1 in ~300 among general population, which is a common disorder, and difficult to diagnose them as FH in children adolescents because of reasons stated previously. On the other hand, homozygous FH is a rare condition, the prevalence of which is estimated to 1 in 160,000 among general population. However, it is of note that state of homozygous FH is an emergent condition, where cardiovascular complications are observed in their adolescence. There are several special treatments for homozygous FH, including microsomal triglyceride transfer protein (MTTP) inhibitor, LDL apheresis, and liver transplantation. Genetic diagnosis for homozygous FH is very important not just because of their diagnosis, but can be useful for their phenotyping. It has been shown that PCSK9 inhibitor, which is quite useful for heterozygous FH, has minimal effect to reduce LDL cholesterol level among the patients with homozygous FH caused by null-type of mutations of LDLR. Other useful points for this matter include assessment of responsiveness to dietary intervention, although dietary interventions typically have minimal influence on LDL cholesterol levels among pediatric patients with FH. Moreover, an important differential diagnosis worth considering in pediatric FH includes sitosterolemia, a disease found to be a phenocopy of homozygous FH. Although patients with sitosterolemia usually exhibit physical xanthomas associated with elevated LDL cholesterol, sitosterolemia is a recessive disorder, with dietary interventions being quite useful for reducing LDL cholesterol levels. Sitosterolemia can be distinguished from FH based on the mentioned important clinical manifestations.

Development of Atherosclerotic Cardiovascular Diseases Among Children and Adolescents with Familial Hypercholesterolemia

FH has been considered one of the major causes of premature ASCVD, with carotid ultrasound being one of the most popular and non-invasive methods for assessing atherosclerosis among pediatric patients with FH. Carotid intima-media thickness (IMT) is often used as a surrogate marker...
for systemic atherosclerosis among not only the general population but also pediatric patients with FH. Moreover, coronary and/or aortic calcium scores have been used to assess early subclinical atherosclerosis, apart from actual plaque accumulation in the coronary artery. Furthermore, arterial stiffness assessed through brachial-ankle pulse wave velocity had been found to be significantly associated with the presence of ASCVD in patients with FH. According to accumulated evidence obtained thus far, the development of ASCVD among patients with FH appears to start during adolescence. These findings have motivated us to consider initiating LDL cholesterol-lowering treatments at an earlier stage of life.

Management of Familial Hypercholesterolemia in Children and Adolescents

Lifestyle interventions should be the fundamental strategy for managing FH in children and adolescents at any age. Statins can be introduced according to guidelines or recommendations. For instance, pitavastatin can be used for Japanese pediatric patients with FH (age ≥10 years) whose LDL cholesterol levels remain ≥180 mg/dL under lifestyle interventions, with the optimal target being set at <140 mg/dL, especially among those with diabetes or a family history of premature ASCVD (Figure 1). There are many studies showing the efficacy and safety regarding the use of statins for children and adolescents, and a meta-analysis and a systemic review are suggesting that it is true. Adherence should be closely monitored among those with poor response to statins before increasing the dose. Adolescent girls should be counseled to suspend statin therapy when contemplating pregnancy. Other medications, such as ezetimibe and resin, can be considered when needed. Notably, the European Atherosclerosis Society had proposed a similar strategy in Europe where “high-risk” pediatric patients with FH aged 8–10 years are recommended to start statins to reduce LDL cholesterol (Figure 2). Moreover, the National Lipid Association expert panel on FH had recommended similar management approaches (Box 3). In addition, resin, and ezetimibe are also shown to effectively reduce LDL cholesterol among the pediatric FH patients. More recently, it has been shown that evolocumab reduced the LDL cholesterol level and other lipid variables among them. Notably, all of the mentioned recommendations have acknowledged the need for actively attempting to diagnose/identify FH in children and adolescents and considering lowering LDL cholesterol levels through lifestyle intervention and statins.

On the other hand, there are other strategies, including MTTP inhibitor (lomitapide), APOB inhibitor ( mipomersen), LDL apheresis, and liver transplantation for the cases with homozygous FH. Another potential medical therapy is Angiopoietin-like 3 (ANGPTL3) inhibitor, whose efficacy and safety for adult patients with homozygous FH has been shown.

Figure 1 Strategies for the management of pediatric familial hypercholesterolemia (FH) (JAS). Green arrows indicate “Yes”; blue arrows indicate “No.” The essential message is that the pediatric patients with FH aged 10 or greater who have low-density lipoprotein cholesterol levels ≥180 mg/dL under appropriate lifestyle intervention may be treated using statins. Reproduced from Harada-Shiba M, Ohita T, Ohsaka A, et al. Joint Working Group by Japan Pediatric Society and Japan Atherosclerosis Society for Making Guidance of Pediatric Familial Hypercholesterolemia. Guidance for Pediatric Familial Hypercholesterolemia 2017. J Atheroscler Thromb. 2018;25(6):S39-S53.37

1. LDL cholesterol should be followed up one month after the initial lifestyle intervention
2. Lifestyle intervention should be continued, LDL cholesterol should be checked ≥3 times/year
3. First choice is statin. Starting from the minimum dose. Target to reduce LDL cholesterol <140 mg/dL for the patients with diabetes, or premature CAD
• Early identification of children with FH ensures that adherence with lifestyle intervention is already established before puberty.
• Children with HeFH should be treated with a fat-modified, heart-healthy diet at diagnosis, and begin statins at age 8-10 years.
• In HoFH, pharmacological treatment should start at diagnosis.
• Early initiation of lifestyle is essential for ensuring long-term adherence.
• Children diagnosed with FH should have lipoprotein(a) [Lp(a)] measured for risk stratification.
• Boys and girls should start treatment at similar ages.
• For children aged 8-10 years, the Panel recommends that LDL-C is ideally reduced by 50% from pre-treatment levels.
• If patients are non-adherent, consider referral to a dedicated, multidisciplinary clinic.
• Children with HoFH should be referred to and cared for at a specialized center.

Figure 2 Strategies for the diagnosis and management of familial hypercholesterolemia (FH) in children and adolescents (EAS). Premature coronary heart disease is defined as a coronary event before age 55 and 60 years in men and women, respectively. Definite FH is defined as genetic confirmation of at least one FH-causing mutation. Close relative is defined as 1st or 2nd degree relatives. Highly probable FH is based on clinical presentation (ie, phenotypic FH): either an elevated low-density lipoprotein cholesterol (LDL-C) level ≥5 mmol/L in a child after dietary intervention or a LDL-C level ≥4 mmol/L in a child with a family history of premature coronary heart disease in close relatives and/or high baseline cholesterol in one parent. Cascade screening from an index case with a FH-causing mutation may identify a child with elevated LDL-C levels ≥3.5 mmol/L. Reproduced with permission from Wiegman A, Gidding SS, Watts GF, et al. European atherosclerosis society consensus panel. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J. 2015;36(36):2425–2437.

Motivation for Genetic Analyses of Familial Hypercholesterolemia and Personalized Medicine for Familial Hypercholesterolemia in Current Clinical Settings

Regardless of its definition, genetic analyses for patients with FH should have clear indications beyond clinical diagnosis. As such, we herein highlight the several advantages of genetic background analysis in FH. First, quite a few patients with hypercholesterolemia have obscure or marginal clinical diagnoses of FH. Moreover, their family history is sometimes quite challenging to obtain. Genetic analyses can definitively identify patients with FH, especially those with traditional monogenic FH. Second, genetic analysis allows us to determine whether patients are heterogeneous or homozygous. Several special medical therapies, such as MTTP inhibitors and LDL apheresis, have typically only been used for homozygous FH in many parts of the world. Moreover, homozygous FH is one of the designated intractable diseases where all medical costs can be covered by the Japanese government, thereby increasing the importance of diagnosis. Third, a portion of patients with FH may have been misdiagnosed as such and actually have another
In the management of FH, genetic analyses involving genes associated with not only LDL cholesterol itself but also ASCVD will become standard. Moreover, target, timing, and LDL cholesterol-lowering therapies will become quite individualized based on genotype, lifestyle, environmental factors, and belief systems. For the earlier identification of patients with FH, nation-wide mass screening, similar to that currently conducted for several other inherited metabolic diseases, such as newborn screening, phenylketonuria, and homocystinuria, will become standard. Furthermore, family history will be automatically assessed to accumulate a huge dataset over the years, which will help us minimize the risk of overlooking children and adolescents with FH (and other inherited diseases).

**Conclusions**

Given that FH is an inherited disease, early diagnosis and intervention can lead to excellent prognosis. Cascade and universal screening appear to be practical strategies for the early identification of patients with FH; however, we need to consider that certain clinical approaches can promote better identification of children and adolescents with FH. Clinical practices and genetic analyses will certainly help improve not only diagnostic accuracy but also risk stratification for personalized medicine.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**


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