

A New Perspective to Improve the Diagnostic Rate of Familial Hypercholesterolemia

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Abstract:

Familial hypercholesterolemia is a genetic disorder characterized by markedly elevated cholesterol levels, skin or tendon xanthomas, and premature coronary atherosclerotic heart disease. The prevalence of the disease is high, but the diagnostic rate is obviously low due to the differences in the clinical diagnostic criteria and the clinical phenotype of patients, or the lack of genetic diagnosis etc. Early diagnosis and early intervention of familial hypercholesterolemia can reduce the occurrence of cardiovascular and cerebrovascular events, so the aim of this review is to explore feasible ways to reduce the missed diagnosis rate of familial hypercholesterolemia.

Keywords:

Familial Hypercholesterolemia, Diagnostic Rate, Xanthomas

1. Introduction

Familial hypercholesterolemia (FH) is a kind of autosomal mutation hereditary disease, which is characterized by significantly elevated levels of low density lipoprotein cholesterol (LDLC), xanthoma of skin or tendon and premature coronary heart disease (CHD), and xanthoma of skin or tendon is a specific sign of FH [1,2]. The mutations of FH include autosomal dominant mutations of LDLR, APOB and PCSK9 genes and rare autosomal recessive mutations of LDLRAP1 and ABCG5/8 genes [3]. At present, there is no internationally recognized clinical diagnostic standard for FH, but the commonly used clinical diagnostic criteria are Dutch Lipid Clinic Network (DLCN) criteria, Simon Broome (SB) criteria and Make early diagnosis-Prevent early death (MED-PED) [4]. Gene detection is still the "gold standard" for the diagnosis of FH, but negative gene results can not completely rule out the possibility of FH. A meta-analysis of more than 7.3 million people based on 62 studies showed that the prevalence of FH in the general population was 1/311, while only about 1% of potential patients could be identified [5]. Obviously the incidence of familial hypercholesterolemia is high, but the diagnostic rate is very low. FH can induce serious cardio-cerebrovascular diseases, so early identification of such patients can intervene as early as possible to reduce the possibility of CHD.

2. Possible Reasons for a Low Diagnostic Rate

Firstly, FH does not have internationally recognized diagnostic criteria. Commonly used diagnostic items include concentrations of cholesterol (total cholesterol and LDLC), skin or tendon xanthomas, family history of hyperlipidemia, and molecular diagnosis. While studies have shown that lipid level in Chinese adults is significantly lower than those in Western populations, so blindly applying diagnostic criteria from Western countries can easily missed diagnosis [6]. In other hand, FH patients with a positive clinical phenotype normally have a higher LDLC level than 190 mg/dl, but a research has indicated that LDLC level were less than 130 mg/dl in 27% of FH gene mutation carriers, so there are limitations to distinguish between FH and non-FH patients [7]. Secondly, High blood lipid levels often present insidiously. Unfortunately, for FH patients, many patients may only seek medical assistance when they experience cardiovascular events such as myocardial infarction, or when they require percutaneous coronary intervention or coronary artery bypass graft surgery. Thirdly, the widespread use of statin drugs has reduced both patients' and physicians' attention to severe hyperlipidemia. Clinical doctors often lack of awareness to inquiry about family history, and patients' recollection of their family history information may be unreliable. Moreover, the complicated scoring system for clinical diagnostic criteria and the high cost of genetic testing contribute to the lower clinical FH diagnosis rate.

3. Feasible Methods to Improve the Diagnostic Rate

3.1. Searching for an appropriate clinical diagnostic model

For patients without a accurate family history, Reinhardt Hesse etc proposed that a machine learning model is a promising tool for screening and diagnosing FH patients. This model only utilizes basic lipid profile, age, and gender to identify genetically confirmed FH in population of suspected FH, which is comparable to the Dutch Lipid Clinic Network criteria [8]. Through the testing of 750,000 patient samples, the Familial Hypercholesterolemia Case Ascertainment Tool (FAMCAT) demonstrates a simple and convenient operation along with a higher identification rate compared to the SB criteria, DLCN criteria, and MED-PED criteria. It achieves a sensitivity rate of 84% and a specificity rate of 60%. The accuracy of FAMCAT in identifying FH is higher than currently recommended methods and can be considered for clinical case detection in patients with severe hypercholesterolemia in primary care [9]. For patients who are taking lipid-lowering drugs and cannot obtain the primary LDLC level, it has been proven that the LDLC correction factor table is very useful in clinical practice, by multiplying the measured LDLC by an appropriate coefficient to obtain an estimated value of untreated LDLC level. And the calculation of the correction factor is based on the analysis of 71 original papers [10].

3.2. The clinical application value of Achilles tendon ultrasound

Skin/tendon xanthomas are specific signs for clinical diagnosis of FH, and the Achilles tendon is the most common site of tendon xanthomas. The formation mechanism of Achilles tendon xanthomas is that macrophages actively ingest circulating low-density lipoproteins and their oxidized low-density lipoproteins to form foam cells and deposit them with free and esterified cholesterol in tendon fibers and surrounding tissues [11]. This sign show the long-term exposure to high cholesterol levels. However, the identification of FH Achilles tendon xanthomas is

based on the clinician's subjective judgment and clinical experience. It is difficult to identify in suspected cases, so Achilles tendon xanthomas should be quantified. Finding an appropriate cutoff value to distinguish FH from non-FH has certain clinical significance. The current imaging examinations for Achilles tendon xanthoma include X-ray, which is a projection technology that cannot reflect the abnormal structure inside the Achilles tendon and expose the patient to radiation [12]. Although magnetic resonance imaging can show the internal structure and lesions of the tendon, but it is expensive and takes a long time to scan [13]. Ultrasound examination is easy to operate, meanwhile it can avoid radiation and reflect the internal condition of the Achilles tendon [14].

Achilles tendon ultrasound is the first choice for detecting Achilles tendon xanthoma in patients with FH, and can provide a certain objective basis for the clinical diagnosis of FH. Commonly used indicators of Achilles tendon ultrasound include Achilles tendon width (ATW), Achilles tendon thickness (ATT) and elasticity index (EI). However, there is still no unified standard. Some studies have proposed that $ATT > 5.3$ mm for women and $ATT > 5.6$ mm for men and $EI < 4.7$ are used as critical values to distinguish FH from non-FH. It can be seen that the combined use of the cutoff values of EI and ATT can improve the FH detection rate [14]. Studies have also shown that among FH gene mutation carriers, ultrasound examination of the Achilles tendon increased the clinical diagnosis of xanthomas from 35 cases (43%) to 55 cases (68%) [15]. 180 participants in the sub-study report from the Lipid transPort disorders Italian GENetic Network (LIPIGEN) who were unable to identify xanthoma of the Achilles tendon during clinical examination were identified through Achilles tendon ultrasound. These patients were successfully identified, resulting in an increased proportion of patients classified as "definite FH" (scoring > 8) from 32.5% to 43.2% [16]. Numerous studies have consistently shown that Achilles tendon ultrasound greatly enhances the diagnostic rate of FH, serving as an indicator of cumulative exposure to blood lipids. Moreover, it can also be utilized for risk prediction of coronary artery disease (CAD). The Achilles tendon ultrasound examination is a safe, reproducible, and cost-effective alternative technique that may be considered for widespread clinical recommendations.

3.3. Genetic testing

Familial hypercholesterolemia is a genetic disease, and genetic testing is the "gold standard", and it is also an important part and supplement of clinical diagnostic criteria. Studies have shown penetrance rates ranging from 73% to 87.5%, and due to gene-environment interactions and gene-epigenetic effectors, patients with FH are clinically phenotypically heterogeneous, and a large number of patients have less severe clinical phenotype, making it difficult for these patients to definite genotype [7,17,18]. Davide Noto etc pointed out that using the DLCN diagnostic criteria to determine "definite FH" (DLCN score > 8) had a mutation gene detection rate of 82% in probands, and a mutation gene detection rate of 78% in their relatives. It is highly likely that the mutation gene detection rates in probands and relatives with "probable FH" (DLCN score 6-8) decreased to 60% and 55%, respectively. The detection rate decreases with decreasing grades, but the absolute number of patients with gene mutations in the "probable FH" is higher than in the "definite FH" ("probable FH" = 124 vs "definite FH" = 93 [19]. K. Haralambos etc also reported that LDLR gene mutations were detected in 13% of patients with a DLCN score < 6 [10]. Genetic testing should not be limited to people with high clinical suspicion of FH, and

extensive genetic screening is still of great significance, which can make up for the lack of clinical diagnosis to a certain extent, reduce the missed diagnosis of patients with negative clinical phenotype of FH, and determine the genetic genotype that can further predict the risk of coronary heart disease, which has guiding significance for treatment. Molecular diagnostics provide clear information that can help patients understand and accept their condition. Although molecular genetic testing is more expensive than clinical diagnosis, it only needs to be done once in lifetime. It has been suggested that the combination of clinical criteria and FH genetic testing may improve diagnostic yields over either method alone [20].

3.4. Cascade screening

Cascade screening is a systematic approach to screening high-risk relatives of probands through lipid screening or genetic testing, which can diagnose patients with FH at a younger age and prevent premature CHD and death. In Norway, 37.6% of high-risk relatives tested positive for genetic screening at the national level, and 35% of all patients with FH gene mutations were diagnosed through cascade screening [21]. In the 10-year plan of FH cascade screening in the Netherlands, genetic testing was conducted on over 60,000 individuals, and over 28,000 individuals were identified to have FH gene mutations, but with the abolition of this active cascade screening method, the number of FH patients detected each year has decreased dramatically from more than 4,000 to less than 500. Cascade screening not only improves the diagnostic rate of FH, but also promotes early initiation of lipid-lowering therapy in FH patients [22]. The extensive cascade screening programs in the Netherlands and Norway both use genetic testing to diagnose high-risk relatives. Compared to using clinical diagnosis, using genetic diagnosis for cascade screening can enable more relatives to receive diagnosis.

3.5. Finding FH patients in the coronary artery disease population

In FH, more than 50% of men by age 50 and more than 30% of women by age 60 will develop fatal or nonfatal coronary artery disease if left untreated [23]. Studies have shown that the prevalence of FH is 18-fold higher in individuals with atherosclerotic cardiovascular disease than in the general population [5]. Multiple studies have reported genetic testing diagnostic rates for FH in early-onset CAD patients ranging from 1.3% [24] to 15.8% [25]. A study in India also showed a prevalence of approximately 23.5% of patients with early-onset CAD diagnosed by the DLCN clinical score [26]. Differences in the scope of these studies may be due to different testing platforms, gene inclusion, age cut-offs for early-onset CAD, LDLC cut-offs, or other traditional CAD risk factors [27], but all of them have found a higher prevalence of FH in people with CAD, so there is a need to raise awareness of FH in this particular population, so that more potential FH patients can be identified and their progression to coronary atherosclerotic heart disease can be prevented.

3.6. Finding FH patients in the juveniles

Juveniles are still an important group that cannot be ignored. A national report in Turkey showed that the prevalence of FH in children and adolescents was 0.37% (1 in 270) and about 0.63% (1:158) in adults [28], indicating that the proportion of FH in children and adolescents remains high. International guidelines recommend starting a heart-healthy diet early in life, with statins starting as the first choice of treatment for children with heterozygous FH (hetFH) at age 6 to 10 years to achieve target levels of

LDLC<130 mg/dL or 50% reduction from baseline. There is an urgent need to identify and treat hetFH in early childhood to maximize treatment efficacy [29]. Ademi et al. found that screening programs for the early detection of FH in juveniles has good investment value from a societal perspective, and that early screening for FH is both healthy and cost-effective compared to no screening and diagnosis and treatment until adulthood [30].

4. Conclusions

Familial hypercholesterolemia is a common “rare disease” that can lead to serious cardiovascular and cerebrovascular diseases, which require early identification and intervention, so it is important to improve the awareness and vigilance of medical workers about this disease. China has a large population base and a large number of undiscovered familial hypercholesterolemia patients. It is necessary to search for clinical diagnostic criteria that meet the requirements of FH patients in China. Strengthening the awareness of clinical physicians to inquire about the family history of hypercholesterolemia patients and promoting the development of Achilles tendon ultrasound and genetic testing which have certain clinical guidance significance for improving the diagnostic rate of familial hypercholesterolemia. Early diagnosis and early intervention of familial hypercholesterolemia can reduce the risk of coronary atherosclerotic heart disease to a certain extent and reduce medical costs.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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References

- [1] M. Michikura, et al. Association between Achilles Tendon Softness and Atherosclerotic Cardiovascular Disease in Patients with Familial Hypercholesterolemia. *Journal of Atherosclerosis and Thrombosis*, 2022, 29(11), 1603-1612.
- [2] A.D. Sniderman, et al. Key Questions About Familial Hypercholesterolemia. *Journal of the American College of Cardiology*, 2022, 79(10), 1023-1031.
- [3] M. Abifadel; C. Boileau. Genetic and molecular architecture of familial hypercholesterolemia. *Journal of Internal Medicine*, 2022, 293(2), 144-165.
- [4] K. Al-Rasadi, et al. 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(2), 85-91.
- [5] P. Hu, et al. Prevalence of Familial Hypercholesterolemia Among the General Population and Patients With Atherosclerotic Cardiovascular Disease. *Circulation*, 2020, 141(22), 1742-1759.
- [6] W. Yang, et al. Serum Lipids and Lipoproteins in Chinese Men and Women. *Circulation*, 2012, 125(18), 2212-2221.

- [7] A.V. Khera, et al. Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia. *Journal of the American College of Cardiology*, 2016, 67(22), 2578-2589.
- [8] R. Hesse, et al. Familial Hypercholesterolemia Identification by Machine Learning Using Lipid Profile Data Performs as Well as Clinical Diagnostic Criteria. *Circulation: Genomic and Precision Medicine*, 2022, 15(5).
- [9] S. Weng, et al. Detection of familial hypercholesterolaemia: external validation of the FAMCAT clinical case-finding algorithm to identify patients in primary care. *The Lancet Public Health*, 2019, 4(5), e256-e264.
- [10] K. Haralambos, et al. Clinical experience of scoring criteria for Familial Hypercholesterolaemia (FH) genetic testing in Wales. *Atherosclerosis*, 2015, 240(1), 190-196.
- [11] S.G. Tsouli, et al. Pathogenesis, detection and treatment of Achilles tendon xanthomas. *Eur J Clin Invest*, 2005, 35(4), 236-44.
- [12] H. Tada, et al. Genetic mutations, regression of Achilles tendon thickness, and cardiovascular events among patients with familial hypercholesterolemia. *Atherosclerosis*, 2022, 340, 28-34.
- [13] F.M.H. James F. Griffith, PhD David K. W. Yeung, PhD Pei Guo, PhD Sik Lok Lam, PhD Fan Xiao, MBChB Defeng Wang, PhD Brian Tomlinson, FRCP. "Achilles Tendon Xanthomas: FatWater separation at Baseline and after Treatment." 2017.
- [14] M. Michikura, et al. Achilles Tendon Softness as a New Tool for Diagnosing Familial Hypercholesterolemia. *JACC: Cardiovascular Imaging*, 2021, 14(7), 1483-1485.
- [15] M. Junyent, et al. The Use of Achilles Tendon Sonography to Distinguish Familial Hypercholesterolemia from Other Genetic Dyslipidemias. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 2005, 25(10), 2203-2208.
- [16] A. Baragetti, et al. Achilles tendon ultrasonography in familial hypercholesterolemia: A sub - study of the LIpid transPort disorders Italian GENetic Network (LIPIGEN). *Journal of Internal Medicine*, 2021, 291(5), 702-704.
- [17] O. Dikilitas, et al. Familial Hypercholesterolemia in the Electronic Medical Records and Genomics Network: Prevalence, Penetrance, Cardiovascular Risk, and Outcomes After Return of Results. *Circulation: Genomic and Precision Medicine*, 2023, 16(2).
- [18] N.S. Abul-Husn, et al. Genetic identification of familial hypercholesterolemia within a single U.S. health care system. *Science*, 2016, 354, 6319.
- [19] D. Noto, et al. Diagnosis of familial hypercholesterolemia in a large cohort of Italian genotyped hypercholesterolemic patients. *Atherosclerosis*, 2022, 347, 63-67.
- [20] B. K. Bellows, et al. Estimated Yield of Screening for Heterozygous Familial Hypercholesterolemia With and Without Genetic Testing in US Adults. *Journal of the American Heart Association*, 2022, 11(11).

- [21] T.P. Leren.; M.P. Bogsrud. The importance of cascade genetic screening for diagnosing autosomal dominant hypercholesterolemia: Results from twenty years of a national screening program in Norway. *Journal of Clinical Lipidology*, 2021, 15(5), 674-681, .
- [22] L. Louter, et al. Cascade screening for familial hypercholesterolemia: Practical consequences. *Atherosclerosis Supplements*, 2017, 30, 77-85.
- [23] D. Marks, et al. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. *Atherosclerosis*, 2003, 168(1), 1-14, .
- [24] D. S. Wald, et al. Prevalence of DNA-confirmed familial hypercholesterolaemia in young patients with myocardial infarction. *European Journal of Internal Medicine*, 2015, 26(2), 127-130,
- [25] C. Pirazzi, et al. High prevalence of genetic determined familial hypercholesterolemia in premature coronary artery disease. *The Application of Clinical Genetics*, 2019, 12, 71-78.
- [26] P. Kumar, et al. Prevalence of familial hypercholesterolemia in patients with confirmed premature coronary artery disease in Ranchi, Jharkhand. *The Egyptian Heart Journal*, 2022, 74, 1.
- [27] E.P. Tricou, et al. Genetic Testing for Familial Hypercholesterolemia in Clinical Practice. *Current Atherosclerosis Reports*, 2023, 25(5), 197-208.
- [28] A. Sonmez, et al. Clinical characteristics of adult and paediatric patients with familial hypercholesterolemia: A real-life cross-sectional study from the Turkish National Database. *Atherosclerosis*, 2023, 375, 9-20.
- [29] F. Mach, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Atherosclerosis*, 2019, 290, 140-205.
- [30] Z. Ademi, et al. Cost-effectiveness and Return on Investment of a Nationwide Case-Finding Program for Familial Hypercholesterolemia in Children in the Netherlands. *JAMA Pediatrics*, 2023, 177, 6.



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