Familial Hypercholesterolemia is Still Underdiagnosed and Undertreated

Familial hypercholesterolemia (FH) is a common genetic cause of premature coronary artery disease (CAD)\(^1\). Making an early diagnosis is essential to prevent early deaths. However, diagnostic rates of heterozygous FH in Japan have not been increased satisfactorily so far.

Intensive lipid-lowering combination therapy is required for many of them to achieve goals of LDL-C. Treatments in FH without a diagnosis are generally insufficient, even in diagnosed FH.

Diagnostic Criteria of FH in JAS and DLCN

To make early diagnoses, spreading awareness and diagnostic criteria of FH in general practice, including primary care, is essential. The simple criteria of the Japan Atherosclerosis Society (JAS)\(^2\) should have superiority on this point compared with complicated scoring criteria of Dutch Lipid Clinic Network (DLCN)\(^3\). DLCN criteria are widely used in Western countries, but some studies reveal that its complexity would limit its usefulness\(^4\). The JAS criteria are similar to other simple Simon–Broome criteria, but the important feature in JAS criteria is X-ray quantification of xanthomas as a standard method.

Quantitative Achilles’ Tendon Evaluation

Tendon/skin xanthomas are the main specific components in diagnosing FH. Reproducible quantification of mild xanthomas is essential for early diagnosis. Mabuchi H. \textit{et al.} reported in 1977 that 9 mm in Achilles’ tendon thickening with X-ray can be used as a discrimination threshold between FH and non-FH and its usefulness in association with CAD\(^5\). The quantification of Achilles’ tendon thickening as standard equipment is a superior feature of the JAS criteria, as DLCN criteria do not adopt the standard quantification for xanthomatosis. Tada H. \textit{et al.} has reported a clinical comparison of criteria between JAS and DLCN. They demonstrated that the JAS 2017 criteria compare favorably with DLCN criteria in sensitivity and specificity\(^3\), possibly because of quantification for xanthomatosis. Nationwide tests for the quantification of Achilles’ tendon thickening is something Japan should be proud of globally.

Lipid Control and Prevalent CAD in FAME study

The recently published FAME study by Yamashita S. \textit{et al.} reported real-world medications for FH in Japan\(^6\). This is one of the large-scale cohort studies of FH in Japan. This study was conducted from the time of the release of ezetimibe, but it did not use PCSK9 inhibitors. The combination of ezetimibe with strong statins is now standard therapy for heterozygous FH. A still-limited use of PCSK9 inhibitors suggests this report would reflect real-world therapy of FH in Japan even now.

At baseline, patients without CAD who had LDL-C $< 100$ mg/dL accounted for 12.3% and those with CAD who had attained the target (LDL-C $< 70$ mg/dL) in the secondary prevention accounted for only 1.8%. Approximately half of the subjects were treated with combination therapies. Most of them were treated with ezetimibe at the end of follow-up. In
most cases, the target level of serum LDL-C was not achieved for primary and secondary prevention of CAD. Even though information about the maximally-tolerated dose of statins was not available in this paper, a considerable portion of study subjects should use PCSK9 inhibitors under the present circumstances7).

CAD was recorded in 23% of patients, and the prevalence of CAD in Japanese patients with heterozygous FH is still very high. This is real world. Primary prevention for childhood with universal screening has just begun in Japan8).

**Achilles’ Tendon Xanthoma in FAME study**

Achilles’ tendon xanthoma was quantitatively evaluated with X-ray in the FAME study. Ogura M. et al. reported that Achilles’ tendon thickening were significantly associated with higher and lower HDL-C and tendency to smoke from the FAME study subanalysis9).

**Heterozygous FH score in FAME study**

FAME study uniquely adopted scoring system “heterozygous FH score,” which is similar to DLCN criteria for assessing the FH phenotype. In heterozygous FH score, all the patients with FH diagnosed with 2017 JAS criteria were diagnosed as definite FH, except for a case with a family history of premature CAD. Other subjects may be included as definite FH who did not meet the 2017 JAS criteria. This paper did not discuss the comparison between heterozygous FH score and 2017 JAS criteria.

Xanthoma or thickening of the Achilles tendon was observed in more than 80% of the patients with X-rays. LDL-C was graded from 1 to 4 points; xanthoma is 6 points, familial history of premature CAD is 4 points, and gene test positive is 8 points. “Definite FH” was defined as heterozygous FH score ≥ 8, and “suspected FH” was diagnosed if the score ranged from 6 to 7.

FAME study evaluated many factors with prevalent CAD in heterozygous FH. In the multiple logistic analysis, male sex, age > 40, heterozygous FH score > 20, hypertension, and sibling CAD were significantly and positively associated with prevalent CAD. In the univariate logistic analysis, xanthoma and low-density lipoprotein receptor mutations were significant but not in the multivariate, presumably because their effects were reflected as an FH score. A heterozygous FH score > 20 might detect very-high-risk FH.

**Definite and Suspected FH**

Definition of “probable” and “possible” FH in DLCN criteria can reflect semi-quantitative certainty as FH. The 2017 JAS criteria do not have such a definition. Nonexperts may be confused about how to treat cases that did not meet JAS criteria: treat as almost equivalent to FH or just non-FH dyslipidemia.

A scoring system can give them an indication of treatment intensity. In the FAME study, “suspected” FH was defined according to the score. Patients with suspected FH were excluded from this paper, but it would be intriguing to assess whether this definition had a clinical impact in Japan.

**Forthcoming JAS Criteria of FH**

For the diagnosis of adult FH, the current 2017 JAS FH criteria showed enough sensitivity and specificity, with careful assessment of tendon xanthomas with a cut-off at 9 mm with X-ray3). Regarding pediatric FH10) or young-adult FH who lack xanthomas, familial studies are essential. The careful evaluation of xanthomas would push up the sensitivity in FH diagnosis. Their average thickness of the Achilles' tendon with X-ray in adults is around 5–7 mm, and mild xanthomas, especially in the young, would not reach 9 mm. Tada H. et al. reported that Achilles’ tendon thickness assessed by X-ray would predict a pathogenic mutation in FH gene. A cut-off value of Achilles’ tendon thickness detected by X-ray is lower than 9.0 mm11).

The Japan Society of Ultrasonics in Medicine and JAS have made a joint statement on “the standard method for measurement of Achilles’ tendon thickness with ultra-sonography for FH screening” in 2018. The measurement with ultrasonography should have more accurate values with reduced errors compared with X-ray12).

Recently, JAS working group for FH criteria proposed the refinement of gender/method-specific thresholds of Achilles’ tendon thickness with X-ray and ultrasonography. This refinement would improve the sensitivity in the next JAS criteria that is planned to go public in 2022.

Gene test for FH is quite useful and feasible as it will detect pathogenic variants in 60%–70% of clinically diagnosed FH but not 100%. Combining clinical and genetic diagnosis will be the best way for severe phenotype FH, cascade study, or other difficult cases in diagnosis. The approval of the FH gene test in the Japanese health insurance system has taken many years.
**Beyond Diagnosis**

To prevent early deaths, efficient identification of a very-high CAD risk group in subjects with FH would be important in the next stage. Diagnosing FH in adults frequently requires coronary examinations, even in asymptomatic cases. It is not difficult for specialists to identify such patients, but it might be difficult for many primary care clinicians.

A high heterozygous FH score in the FAME study showed association with CAD prevalence\(^5\). Scoring components can reflect CAD risk. LDL-C scoring criteria are associated with long-term mortality in the general population\(^13\). It has been well established that familial histories of CAD are also an independent risk. Presence of xanthomas is associated with increased CAD risk in FH\(^3, 5, 9\). The identification of pathogenic variants in FH genes is associated with increased CAD risk in FH\(^14\). It is reasonable to assume that the FH score can be used to detect very-high-risk groups.

Santos RD. \textit{et al}. proposed a definition of “severe FH” based on untreated LDL-C levels and individual’s responsiveness to conventional lipid-lowering drugs\(^15\). This definition was proposed mainly on overlapping phenotype among heterozygous and homozygous FH, but responsiveness to lipid-lowering drugs also might be used for further risk assessment.

FAME study demonstrated clinical challenges to overcome in subjects with FH in Japan: high prevalence of CAD and an insufficient lipid control in primary and secondary prevention\(^6\). Considerable cases should be indicated for the PCSK9 inhibitors now.

Unique FH scoring in the FAME study showed some possibility that may have a role in risk assessment for CAD beyond diagnosis in FH.

Fully enforcing early diagnosis from childhood will conquer CAD prevalence, but we still have a long way to go.

**Conflicts of Interest**

None.

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