Committee Report 9

Familial Hypercholesterolemia

Executive Summary of the Japan Atherosclerosis Society (JAS) Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases in Japan — 2012 Version

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This is a collaborative work to describe the guidelines for familial hypercholesterolemia issued by the Committee for Epidemiology and the Clinical Management of Atherosclerosis, the Committee for the Diagnosis and Treatment of Familial Hypercholesterolemia and the Research Committee for Primary Hyperlipidemia, Research on Measures against Intractable Diseases.

Heterozygous Familial Hypercholesterolemia

1. Condition and Clinical Picture of FH

Familial hypercholesterolemia (FH) is an autosomal dominant disease caused by abnormal LDL receptors or LDL receptor-related genes, characterized by the triad of (1) hyper-LDL cholesterolemia, (2) premature coronary artery disease (CAD) and (3) tendon/cutaneous xanthoma. Arcus corneae is also characteristic of FH; however, the rate is approximately 30%.

FH by itself is a very high-risk condition for CAD. Untreated men 30 to 50 years of age and

women 50 to 70 years of age are likely to develop CAD, such as myocardial infarction and angina pectoris¹⁾. Early diagnosis and appropriate treatment result in the prevention of premature death. Heterozygous FH exists in approximately one in 500 people, and it is estimated that there are approximately 300,000 patients in Japan. Therefore, heterozygous FH is one of the genetic diseases most frequently encountered by general practitioners.

2. Diagnosis of Heterozygous FH

1) LDL-C Cutoff Value

Table 1 shows the diagnostic criteria. Using data obtained from a total of 1,397 untreated dyslipidemic patients, including 439 patients with FH and 958 patients without FH, an analysis was performed of

Table 1. Diagnostic Criteria for Heterozygous FH in Adults (15 Years of Age or Older)

1. Hyper-LDL cholesterolemia (an untreated LDL-C level of ≥ 180 mg/dL)
2. Tendon xanthoma (tendon xanthoma on the backs of the hands, elbows, knees, etc. or Achilles tendon hypertrophy) or xanthoma tuberosum
3. Family history of FH or premature CAD (within the patient's second-degree relatives)

- The diagnosis should be made after excluding secondary hyperlipidemia
- If a patient meets two or more of the above-mentioned criteria, the condition should be diagnosed as FH. In cases of suspected FH, obtaining a diagnosis using genetic testing is desirable.
- Xanthoma palpebrarum is not included in xanthoma tuberosum.
- Achilles tendon hypertrophy is diagnosed if the Achilles tendon thickness is ≥ 9 mm on soft X-ray imaging.
- An LDL-C level of ≥ 250 mg/dL strongly suggests FH.
- If a patient is already receiving drug therapy, the lipid level that led to treatment should be used as the reference for diagnosis.
- Premature CAD is defined as the occurrence of CAD in men < 55 years of age or women < 65 years of age.
- If FH is diagnosed, it is preferable to also examine the patient's family members.

major items, including an LDL-C level of ≥ 180 mg/dL, the presence of Achilles tendon hypertrophy or cutaneous xanthoma and a history of FH or premature CAD in relatives within the second degree. The results showed a sensitivity of 94.3% and a specificity of 99.1%. In cases involving an LDL-C level of ≥ 190 mg/dL, the sensitivity was 92.1% and the specificity was 99.1%. Therefore, 180 mg/dL, the level at which the specificity was the same and the sensitivity was higher than that observed at 190 mg/dL, was adopted as the LDL-C cutoff value²⁾. Because this analysis showed that 5% of patients with an LDL-C level of ≥ 250 mg/dL do not have FH, a diagnosis of FH is thus strongly suspected in the presence of an LDL-C level of ≥ 250 mg/dL alone³⁾.

2) Soft X-Ray Radiography of the Achilles Tendon

Achilles tendon hypertrophy should be evaluated using soft X-ray radiography. Positioning is performed so that the lower leg bones and sole of the foot form a 90-degree angle, and radiation is administered so that the X-ray enters the center of the lateral malleolus from the side of the foot. The imaging distance should be 120 cm, and the imaging conditions should be 50 kV and 5.0 mA. When the greatest dimension is ≥ 9 mm, hypertrophy is diagnosed. Conducting the evaluations using ultrasonography is possible, although it has not yet been standardized.

3) Differential Diagnosis

Diseases that must be distinguished from FH include conditions that cause secondary hyperlipidemia (e.g., diabetes mellitus, hypothyroidism and nephrotic syndrome) and a similar disease, familial combined hyperlipidemia (FCHL). FCHL is distinguished by the absence of tendon xanthoma, the presence of small, dense LDL, the presence of other types of dyslipidemia (types IIa, IIb and IV) in the patient's family and, in children, a lower degree of increase in the LDL-C level compared with that observed in FH.

3. Management Targets for LDL-C in Heterozygous FH

Because FH is a disease associated with a very high risk of CAD, FH should be considered to correspond to secondary prevention, and it is desirable to set a management target for the LDL-C level at < 100 mg/dL. However, in many cases, it is difficult to achieve a management target for an LDL-C level of < 100 mg/dL in FH patients in clinical practice. Therefore, it is acceptable to aim for $< 50\%$ of the pretreatment level if the management target for LDL-C is not achieved. The achievement of the management target does not always assure the absence of future cardiovascular events. In the treatment of FH, risk assessment cannot be applied using the risk charts provided in these guidelines. This management target should be applied to patients with FH ≥ 30 years of age, and it is desirable to administer the treatment under the direction of a specialist, in principle. Treatment for FH in patients 15-29 years of age must be administered under the direction of a specialist.

4. Treatment of Heterozygous FH

1) Lifestyle Modification

Lifestyle modification should be performed in FH patients after diagnosis and continued as described in committee report 7A⁴⁾. However, due to the high risk of cardiovascular disease (CVD), screening for CVD before administering exercise therapy is essential. CVD should be evaluated using patient interviews to determine the presence or absence of effort angina, and exercise electrocardiography and echocardiography should be performed. If the existence of ischemic heart disease is suspected, administering treatment for ischemic heart disease before initiating exercise therapy is thus preferred. Smoking cessation and obesity management are also important.

2) Drug Therapy

Statins are the first-line drugs for FH treatment. A retrospective analysis of 329 patients with heterozy-

gous FH conducted in Japan revealed that the use of statins delayed the onset of CAD⁵⁾. If the patient does not respond to monotherapy with statins, other lipid-lowering drugs should be concomitantly used. Such concomitant drugs include ezetimibe, bile acid-binding resins (cholestyramine and colestimide), probucol, fibrates and nicotinic acid derivatives. Although there is no evidence that these combination therapies inhibit cardiovascular events in patients with FH more effectively than statin monotherapy, strict management of the LDL-C level is recommended in patients with FH. A retrospective investigation suggested that probucol delays the recurrence of CAD in patients with heterozygous FH⁶⁾.

3) Indications for LDL Apheresis

In heterozygous FH patients, LDL apheresis should be considered if the total cholesterol (TC) level does not decrease to ≤ 250 mg/dL following intensive drug treatment in the presence of CAD. If LDL apheresis is indicated, it is desirable to consult a specialist.

5. FH in Children

1) Diagnosis of Heterozygous FH in Children

The initial finding of heterozygous FH is hyper-LDL cholesterolemia. In childhood, many patients do not develop physical signs associated with hyper-LDL cholesterolemia, such as Achilles tendon xanthoma and arcus corneae. Therefore, FH in children is primarily diagnosed based on the presence of hyper-LDL cholesterolemia and family history. In the diagnosis of FH in children, if the parent(s) has/have hyper-LDL cholesterolemia, a diagnosis of FH in the parent(s) should be established. The diagnostic criteria for heterozygous FH in children are shown in **Table 2**. Because 95% of healthy children have an LDL-C level of ≤ 140 mg/dL⁷⁾, the cutoff value for screening is defined as 140 mg/dL.

2) Treatment for Heterozygous FH in Children

• Nutritional Guidance and Lifestyle Modification

If heterozygous FH is diagnosed, the affected child and their guardians should be directed to modify their lifestyle as soon as possible. Affected children with a smoking habit should be directed to stop smoking. In addition, they should be directed to avoid smoking throughout their life and receive an explanation of the risk of passive smoking; their family members should also be directed to stop smoking.

• Drug Therapy

Evidence pertaining to the age from which treat-

Table 2. Diagnostic Criteria for Heterozygous FH in Children

1. Hypercholesterolemia: an untreated LDL-C level of ≥ 140 mg/dL (measure the LDL-C level if the TC level is ≥ 220 mg/dL)
2. Family history of FH or premature CAD within the patient's second-degree relatives

- Pediatric patients exhibit few symptoms, such as tendon xanthoma. Therefore, diagnosing FH in the patient's family members is important.
- The LDL-C level may vary during development. Providing careful follow-up is necessary.
- Premature CAD is defined as the occurrence of CAD in men < 55 years of age or women < 65 years of age.

ment should be administered in patients with heterozygous FH has not yet been established in Japan. Because atherosclerotic changes in the coronary arteries are observed from an earlier age in heterozygous FH patients, appropriate LDL-C management is recommended at an earlier age. According to the proposal of the American Academy of Pediatrics, if a patient has an "LDL-C level of ≥ 190 mg/dL" or an "LDL-C level of ≥ 160 mg/dL and a family history of premature CAD or at least two risk factors," lipid-lowering treatment should be initiated, even in children, and if lifestyle modification is inadequate, drug therapy should also be considered in boys aged 8 to 10 years or older and in girls after menarche⁸⁾. Among patients who are at a very high risk, such as patients with tendon xanthoma or aortic stenosis or those with a family history of remarkable atherosclerosis, a differential diagnosis of heterozygous FH should be performed. With respect to drug therapy, in terms of safety for growth and development, bile acid-binding resins, which are not absorbed from the gastrointestinal tract, are typically used and are the first-line drugs. Drug therapy for children should be administered under the direction of a specialist.

6. Heterozygous FH in Women

Drug therapy, other than bile acid-binding resins, during pregnancy should be carefully considered due to concerns regarding the risk of fetal malformations. According to the National Institute for Health and Clinical Excellence⁹⁾, if pregnancy is diagnosed during drug therapy, lipid-lowering drugs other than bile acid-binding resins should be immediately discontinued, and, if there is a possibility of pregnancy, pregnancy after the discontinuation of drug treatment for three months should be recommended.

Homozygous Familial Hypercholesterolemia

1. Diagnosis of Homozygous FH

Homozygous FH is characterized by the presence of a TC level of ≥ 600 mg/dL, xanthoma and CVD from childhood, with both parents being heterozygous for FH. Therefore, making a clinical diagnosis is possible. If homozygous FH is suspected even when the TC level is < 600 mg/dL, obtaining the diagnosis and therapeutic decisions from a specialist is essential.

2. Drug Therapy for Homozygous FH

Similar to that recommended for patients with heterozygous FH, lifestyle modification, including diet therapy, exercise therapy, smoking cessation and obesity management, provides the basis for treatment in patients with homozygous FH, although intensive LDL-C-lowering treatment is required at an earlier age because patients with homozygous FH face a considerable risk with respect to the development and progression of CAD. However, homozygous FH is much less responsive to drug treatment than heterozygous FH. Therefore, the administration of LDL apheresis once every one to two weeks is necessary. Probucol exerts LDL-C-lowering effects on homozygous FH and may cause the regression or disappearance of xanthoma in the skin or Achilles tendon. For patients with homozygous FH who wish to have children, screening for CAD and the presence of aortic stenosis and supralvalvular stenosis should be performed, and appropriate measures should be taken as required to ensure the safe continuation of pregnancy and delivery¹⁰.

3. LDL Apheresis for Homozygous FH

In patients with homozygous FH, it is difficult to decrease the LDL-C level sufficiently using existing drug therapies, and many patients require continued LDL apheresis with extracorporeal circulation starting in childhood. Considering the inhibition of the progression of CVD, the earlier LDL apheresis is initiated, the better; however, it is difficult to perform LDL apheresis until the affected child can be kept in bed during apheresis. Realistically, the timing of treatment initiation is 4 to 6 years of age, when children can lie in bed and extracorporeal circulation can be performed; however, it is recommended that the treatment be initiated as early as possible.

4. Pregnancy and Delivery of Patients with Homozygous FH

It is important to permit patients with homozygous FH to become pregnant as planned. Before preg-

nancy, screening for atherosclerosis should be performed using carotid ultrasonography, echocardiography and exercise tolerance tests to assess the status of atherosclerosis. By three months before the planned pregnancy, treatment with lipid-lowering drugs other than bile acid-binding resins should be discontinued. Because the cardiovascular system is greatly stressed during late pregnancy, particularly at delivery, performing LDL apheresis during pregnancy is desirable. LDL apheresis can also be safely administered during pregnancy.

5. Homozygous FH Designated as a Specified Disease

In October 2009, homozygous FH was designated as a specified disease in the Specified Disease Treatment Research Program. The criteria for designation are as follows: patients with homozygous FH definitively diagnosed using a genetic analysis of genes involved in the LDL metabolic pathway or measurement of the LDL receptor activity are definitively designated, and patients with remarkable hypercholesterolemia and those with cutaneous xanthoma starting in childhood who are refractory to drug treatment should be designated.

Footnotes

This is an English version of the guidelines of the Japan Atherosclerosis Society (chapter 9) published in Japanese in June, 2012. The details of this Committee Report 9 on Familial Hypercholesterolemia have been previously published as an original manuscript¹¹; this is a brief summary.

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