

Homozygous Familial Hypercholesterolemia

Atsushi Nohara¹, Hayato Tada², Masatsune Ogura³, Sachiko Okazaki⁴, Koh Ono⁵, Hitoshi Shimano⁶, Hiroyuki Daida⁷, Kazushige Dobashi⁸, Toshio Hayashi⁹, Mika Hori¹⁰, Kota Matsuki¹¹, Tetsuo Minamino¹², Shinji Yokoyama¹³, and Mariko Harada-Shiba¹⁴ on behalf of the Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the Ministry of Health, Labour and Welfare of Japan[†]

¹Department of Clinical Genetics, Ishikawa Prefectural Central Hospital, Kanazawa, Japan

²Department of Cardiovascular Medicine, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan

³Department of Molecular Innovation in Lipidology, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan

⁴Division for Health Service Promotion, The University of Tokyo, Tokyo, Japan

⁵Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan

⁶Department of Internal Medicine (Endocrinology and Metabolism), Faculty of Medicine University of Tsukuba, Tsukuba, Japan

⁷Faculty of Health Science, Juntendo University, Juntendo University Graduate School of Medicine, Tokyo, Japan

⁸Department of Pediatrics, School of Medicine, University of Yamanashi, Yamanashi, Japan

⁹School of Health Sciences, Nagoya University Graduate School of Medicine, Nagoya, Japan

¹⁰Department of Endocrinology, Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan

¹¹Department of Endocrinology and Metabolism, Hirosaki University Graduate School of Medicine, Hirosaki, Japan

¹²Department of Cardiorenal and Cerebrovascular Medicine, Faculty of Medicine, Kagawa University, Kagawa, Japan

¹³Institute for Biological Functions, Chubu University, Aichi, Japan

¹⁴Department of Molecular Pathogenesis, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan

[†]**The Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the Ministry of Health, Labour and Welfare of Japan:** Mariko Harada-Shiba (Department of Molecular Pathogenesis, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan), Shun Ishibashi (Division of Endocrinology and Metabolism, Department of Internal Medicine, School of Medicine, Jichi Medical University, Tochigi, Japan), Shinji Yokoyama (Institute for Biological Functions, Chubu University, Aichi, Japan), Hitoshi Shimano (Department of Internal Medicine (Endocrinology and Metabolism), Faculty of Medicine University of Tsukuba, Tsukuba, Japan), Koutaro Yokote (Department of Endocrinology, Hematology and Gerontology, Chiba University Graduate School of Medicine, Chiba, Japan), Hideaki Bujo (Department of Clinical-Laboratory and Experimental-Research Medicine, Toho University Sakura Medical Center, Chiba, Japan), Shizuya Yamashita (Rinku General Medical Center, Osaka, Japan), Kazuhisa Tsukamoto (Department of Internal Medicine, Teikyo University, Tokyo, Japan), Toshio Hayashi (School of Health Sciences, Nagoya University Graduate School of Medicine, Nagoya, Japan), Katsunori Ikekawa (Division of Neurology, Anti-Aging, and Vascular Medicine, Department of Internal Medicine, National Defense Medical College, Saitama, Japan), Takanari Gotoda (Department of Metabolic Biochemistry, Faculty of Medicine, Kyorin University, Tokyo, Japan), Kazushige Dobashi (Department of Pediatrics, School of Medicine, University of Yamanashi, Yamanashi, Japan), Yoshihiro Miyamoto (Open Innovation Center, National Cerebral and Cardiovascular Center, Osaka, Japan), Misa Takegami (Department of Preventive Medicine and Epidemiology, National Cerebral and Cardiovascular Center, Osaka, Japan), Yoshiki Sekijima (Department of Medicine (Neurology & Rheumatology), Shinshu University School of Medicine, Matsumoto, Japan), Yasushi Ishigaki (Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Iwate Medical University, Iwate, Japan), Hiroaki Okazaki (Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan), Atsushi Nohara (Ishikawa Prefectural Central Hospital, Kanazawa, Japan), Shingo Koyama (Division of Neurology and Clinical Neuroscience, Department of Internal Medicine III, Yamagata University Faculty of Medicine, Yamagata, Japan), Kyoko Inagaki (Division of Diabetes, Endocrinology, and Metabolism, Department of Medicine, Nippon Medical School, Tokyo, Japan), Koh Ono (Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan), Masahiro Koseki (Division of Cardiovascular Medicine, Department of Medicine, Osaka University Graduate School of Medicine, Osaka, Japan), Hiroyuki Daida (Faculty of Health Science, Juntendo University, Juntendo University Graduate School of Medicine, Tokyo, Japan), Manabu Takahashi (Division of Endocrinology and Metabolism, Department of Internal Medicine, Jichi Medical University, Tochigi, Japan), Kimitoshi Nakamura (Department of Pediatrics, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan), Takashi Miida (Department of Clinical Laboratory Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan), Masa-aki Kawashiri (Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kanazawa University, Kanazawa, Japan), Tetsuo Minamino (Department of Cardiorenal and Cerebrovascular Medicine, Faculty of Medicine, Kagawa University, Kagawa, Japan), Sachiko Okazaki (Division for Health Service Promotion, The University of Tokyo, Tokyo, Japan), Hayato Tada (Department of Cardiovascular Medicine, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan), Jun Wada (Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University

Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan), Masatsune Ogura (Division of Lipid Metabolism, Department of Molecular Innovation in Lipidology, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan), Hirotohi Ohmura (Department of Cardiovascular Medicine, School of Medicine, Juntendo University, Tokyo, Japan), Mika Hori (Department of Endocrinology, Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan), Kota Matsuki (Department of Endocrinology and Metabolism, Hirosaki University Graduate School of Medicine, Hirosaki, Japan), Masashi Yamamoto (Department of Endocrinology, Hematology and Gerontology, Chiba University Graduate School of Medicine, Chiba, Japan), Yasuo Takeuchi (Division of Nephrology, Kitasato University School of Medicine, Kanagawa, Japan), Atsuko Nakatsuka (Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan), Daisaku Masuda (Department of Cardiology, Health Care Center, Rinku Innovation Center for Wellness Care and Activities (RICWA), Rinku General Medical Center, Osaka, Japan), Satoshi Hirayama (Department of Clinical Laboratory Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan), Masayuki Kuroda (Center for Advanced Medicine, Chiba University Hospital, Chiba University, Chiba, Japan), Takashi Yamaguchi (Center of Diabetes, Endocrinology and Metabolism, Toho University Sakura Medical Center, Chiba, Japan), Takeyoshi Murano (Clinical Laboratory Program, Faculty of Science, Toho University, Chiba, Japan).

Familial hypercholesterolemia (FH) is an inherited disorder with retarded clearance of plasma LDL caused by mutations of the genes involved in the LDL receptor-mediated pathway and most of them exhibit autosomal dominant inheritance. Homozygotes of FH (HoFH) may have plasma LDL-C levels, which are at least twice as high as those of heterozygous FH (HeFH) and therefore four times higher than normal levels. Prevalence of HoFH had been estimated as 1 in 1,000,000 before but more recent genetic analysis surveys predict 1 in 170,000 to 300,000. Since LDL receptor activity is severely impaired, HoFH patients do not or very poorly respond to medications to enhance activity, such as statins, and have a poorer prognosis compared to HeFH. HoFH should therefore be clinically distinguished from HeFH. Thorough family studies and genetic analysis are recommended for their accurate diagnosis.

Fatal cardiovascular complications could develop even in the first decade of life for HoFH, so aggressive lipid-lowering therapy should be initiated as early as possible. Direct removal of plasma LDL by lipoprotein apheresis has been the principal measure for these patients. However, this treatment alone may not achieve stable LDL-C target levels and combination with drugs should be considered. The lipid-lowering effects of statins and PCSK9 inhibitors substantially vary depending on the remaining LDL receptor activity of individual patients. On the other hand, the action of an MTP inhibitor is independent of LDL receptor activity, and it is effective in most HoFH cases.

This review summarizes the key clinical issues of HoFH as well as insurance coverage available under the Japanese public healthcare system.

Key words: Homozygous familial hypercholesterolemia, Family study, Genetic diagnosis, Lipoprotein apheresis, MTP inhibitor, PCSK9 inhibitor, Cutaneous and Tendon Xanthoma, Aortic Supra-valvular stenosis

Introduction

Familial hypercholesterolemia (FH) is an inherited disorder of lipoprotein metabolism caused by mutations of the genes involved in the LDL receptor-mediated pathway for cellular uptake of LDL. Most FH patients show an autosomal dominant trait. Hyper-LDL-cholesterolemia remains throughout their lives and causes premature coronary heart disease unless properly treated¹⁻³.

Early diagnosis and initiation of lipid-lowering therapy is essential for preventing development of cardiovascular complications, even in Japan where cardiovascular disease is not the leading cause of death and its prevalence among FH patients seems to be somewhat lower than in Western countries. Heterozygous FH (HeFH) patients who carry the mutated gene in a single allele have plasma LDL cholesterol (LDL-C) levels double normal or higher and may experience the first cardiovascular event as

Address for correspondence: Atsushi Nohara, Department of Clinical Genetics, Ishikawa Prefectural Central Hospital, 2-1 Kuratsuki-Higashi, Kanazawa, Ishikawa 920-8530, Japan E-mail: atsushinohara@mac.com

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A 3-year-old patient:
wrists, knees, ankles

Adult cases:
fingers, buttocks, Achilles tendon

Fig. 1. Cutaneous and Tendon Xanthomas in HoFH

Presence of cutaneous xanthomas from childhood is strongly suggestive of HoFH, and tendon xanthomas are generally prominent in adults with HoFH.

early as their thirties. With mutations in both alleles, homozygous FH (HoFH) exhibits LDL-C levels twice those of HeFH, or even higher, and patients develop cardiovascular complications even in the first decade of their lives. Most HoFH is refractory to statins and other standard lipid-lowering drugs as most of them depend on remaining LDL receptor activity. Thus, HoFH has a poor prognosis compared to HeFH and therefore, earlier diagnosis and more aggressive treatments are required to prevent premature death.

1. Clinical Manifestations of HoFH

Familial hypercholesterolemia (FH) is a disease with a triad of clinical characteristics: elevated LDL-C, cutaneous and/or tendon xanthomas, and premature atherosclerotic cardiovascular disease (ASCVD). A genetic defect in LDL receptor function is the cause of FH, and activity of the LDL receptor is completely or almost completely absent in HoFH patients. HoFH includes homozygotes or compound/double heterozygotes of autosomal-dominant disease-

causing mutations in the related genes, and their parents are HeFH, but there are rare exceptions that exhibit autosomal recessive inheritance^{4,5}.

1) Elevated LDL-C Levels

HoFH patients have very high LDL-C levels from birth, which puts them at very high-risk of coronary heart disease. Plasma LDL-C levels are more than 500 mg/dL in many cases of genetically confirmed HoFH, but there is considerable variation in lipid levels among patients. Those with LDL-C levels over 370 mg/dL (or total cholesterol levels over 450 mg/dL) in the fasting steady state should consult with specialists as they are probably cases of HoFH.

2) Cutaneous and Tendonous Xanthomas (Fig. 1)

Characteristic cutaneous xanthomas that have developed since infancy are physical findings suggestive of HoFH. They are commonly found on the extensor surfaces of the elbows/knees and wrist/gluteal regions and parents often take a child to a

doctor for the first visit because of them⁶). Tendon xanthomas are pathognomonic for both HeFH and HoFH, but not apparent during childhood and gradually appear around puberty. Xanthomas can be repressed or made to regress with continuous aggressive lipid-lowering treatment.

3) ASCVD

The prognosis for untreated HoFH is extremely poor. It is difficult for patients to live beyond 30 years without treatment. The LDL-C accumulation threshold hypothesis, which uses a calculation of [LDL-C x years of life], has been proposed as a rational explanation for the coronary risk of FH, and according to it, the coronary threshold of HoFH would be around 11 years old even for individuals with lower LDL-C levels⁷). Angina or myocardial infarction from infancy, as well as aortic supra- and/or valvular stenosis are often noted in HoFH (Fig. 2), and may become the main cause of death in patients. Even with substantially effective treatment, systemic atherosclerosis, with such manifestations as aortic aneurysms, peripheral artery disease, and cerebrovascular disease, develops along with aging. Aggressive LDL-lowering treatments should be started as young as possible to prevent these atherosclerotic complications.

2. Prevalence

In the 1970s, prevalence of HeFH was estimated as 1 in 500 in the general population, and accordingly, that of HoFH as 1 in 1,000,000⁸). However, more recent molecular genetic studies have revealed that FH is more common than previously expected. HeFH is now estimated as 1 in 200 to 300 and HoFH as 1 in 170,000 to 300,000 in many countries including Japan⁹⁻¹³).

3. Genetics

LDL receptor-related disease-causing mutations are identified only in 60 to 80% of clinically diagnosed HeFH¹⁴⁻¹⁶). Most of them are in the LDL receptor gene (*LDLR*), and those in apolipoprotein B-100 (coded as *APOB* gene), the main ligand for the LDL receptor, have also been reported mainly in Caucasian populations¹⁷). In 2003, gain-of-function mutations in *PCSK9*, the gene coding proprotein convertase subtilisin/kexin-type 9 and enhancer of LDL receptor degradation, were found. This was considered to be the second major FH-related gene, explaining 5% of HeFH in Japan¹⁸).

Families with FH caused by mutations in *LDLR*, *APOB*, and *PCSK9* all show autosomal dominant inheritance. Since *LDLR* accounts for the majority of

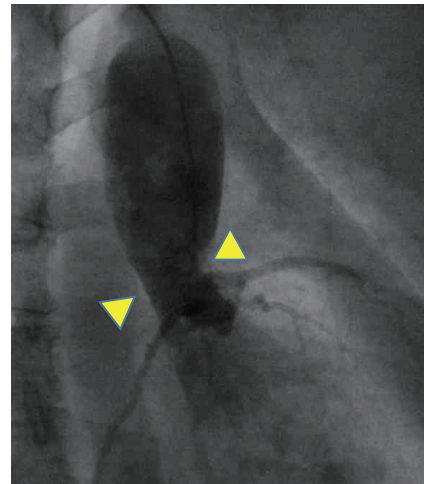


Fig. 2. Aortic Supra-valvular stenosis in HoFH

Supra-valvular stenosis is a pathognomonic finding of HoFH, and one of the causes of premature cardiac death in this disease.

the FH mutations, most individuals with HoFH are “true homozygotes” or “compound heterozygotes” for two different mutations in *LDLR*. Some patients are “double heterozygotes”, having combined mutations in *LDLR* and *PCSK9*⁴), for example. The parents of HoFH children who are “true or compound heterozygotes” mostly show the HeFH phenotype. On the other hand, the family traits of HoFH “double heterozygotes” may not apparently exhibit simple Mendelian inheritance since the heterozygotes for *PCSK9* show a variety of phenotypes.

It should be noted that HeFH is underdiagnosed and undertreated in the general population³). In the background of one suspected case of HoFH, there are many family members with HeFH, and they must be properly cared for in time to prevent their premature death.

Besides the mutations discussed above, those causing, autosomal recessive hypercholesterolemia (ARH), a rare unique type of FH have been reported in Japan^{4, 5}). ARH is caused by mutations in a gene coding low-density lipoprotein receptor adaptor protein 1 (*LDLRAP1*). *LDLRAP1* is an adaptor protein making a complex with clathrin and LDL receptors for efficient endocytosis of LDL receptors. Heterozygous carriers of this mutation do not exhibit the HeFH phenotype so it apparently shows autosomal recessive inheritance. If the parents in a probable case of HoFH have normolipidemia, ARH may be considered.

Disease-causing mutations cannot be identified in 20% to 40% of clinically diagnosed HeFH¹⁹). This may be due to still-unknown FH-related genes or limitations of analytic technologies. A clinical

Table 1. Diagnostic criteria for FH in children

<ol style="list-style-type: none"> 1. Elevated serum LDL cholesterol levels: untreated LDL-C level of ≥ 140 mg/dL (If total cholesterol level is ≥ 220 mg/dL, measure LDL-C level) 2. Family history of FH or premature CAD (within second-degree relatives)
<ul style="list-style-type: none"> • Secondary hyperlipidemia should be ruled out. • If a patient meets both of the above-mentioned criteria, FH is diagnosed. • As LDL-C levels fluctuate during growth due to dietary and hormonal influences, careful examination is required. • Clinical symptoms and findings including angina, xanthomas, and corneal arcus are rare in heterozygous FH children. Therefore, family history of FH is important in making diagnosis • Premature CAD is defined as occurrence of CAD in men < 55 years old or in women < 65 years old. • Homozygous FH should be suspected if patient has xanthomas.

Table 2. Diagnostic criteria for heterozygous FH in adults (15 years of age or older)

<ol style="list-style-type: none"> 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)
<ul style="list-style-type: none"> • 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 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, respectively. • If FH is diagnosed, it is preferable to also examine the patient's family members.

diagnosis of typical HoFH cannot be excluded even if two pathogenic FH gene variants are not identified. A substantial portion of HeFH cases without “known” FH-gene mutations could be “polygenic hypercholesterolemia”²⁰⁾ or “oligogenic FH”²¹⁻²³⁾, though these concepts of FH have not become established. Although genetic analysis provides a definitive diagnosis of HoFH, the possibility of such cases cannot be excluded. Therefore, clinical assessment including thorough physical examination and familial studies is essential. For information, Japanese public healthcare insurance does not cover the expenses for HoFH genetic testing as of February 2021.

4. Pathophysiology

LDL receptor activity is completely or nearly all lost in HoFH. Severely elevated LDL-C levels from birth (more exactly, from fetal period²⁴⁾) often cause fatal cardiovascular disease even in infancy. As an example of cholesterol deposition in tissues, pathognomonic skin xanthomas develop from infancy in HoFH and tendon xanthomas become apparent later, and they are more prominent than those in HeFH.

5. Diagnostic Criteria in Japan

1) Clinical Diagnosis

A clinical diagnosis of HoFH can be made on the basis of skin or tendon xanthomas since infancy, and untreated LDL-C levels of twice those of HeFH or higher. Diagnostic criteria for FH in Japanese guidelines apply not only HeFH but also HoFH^{1, 4)} (Table 1, Table 2). In cases with very high LDL-C and/or prominent xanthomas, HoFH should be suspected^{25, 26)}.

Skin xanthomas since infancy are pathognomonic for HoFH, and sometimes the chief complaint for the first consultation with doctors⁴⁾ (Fig. 1). Skin xanthomas in pediatric HoFH are frequently found in flexures of the wrist and ankles, and also in other regions having mechanical stress. Tendon xanthomas are more prominent than in HeFH²⁷⁾, but become apparent later than skin xanthomas.

Typical HoFH exhibits total cholesterol levels of more than 600 mg/dL in total¹⁾, but there is considerable overlapping of levels between HoFH and severe HeFH²⁸⁾. LDL-C levels over 370 mg/dL (or total cholesterol levels over 450 mg/dL) in the fasting steady state would be sufficient for a diagnosis of probable HoFH and the patient should be referred to

specialists. In pediatric patients, plasma LDL-C levels may fluctuate and should be measured multiple times.

Measurement of LDL receptor activity in the fibroblasts of patients provides useful information in diagnosing HoFH, but is currently not routinely available at the laboratories of commercial or research facilities in Japan. Assaying LDL receptor activity in lymphocytes is feasible²⁹⁾ but less reliable than fibroblast measurements.

2) Genetic Diagnosis

Genetic testing is recommended for suspected HoFH cases, but is not covered by Japanese public healthcare insurance as of February 2021. Genetic diagnosis indicates the potential efficacy of drug treatment and thereby therapeutic strategies^{30, 31)}. Conversely, drug ineffectiveness (for example, refractory to PCSK9 inhibitors) may suggest the HoFH genotype so genetic tests should be considered in such cases³²⁾.

The possibility of detecting an FH-causative mutation in HeFH is 60 to 80%. Therefore, diagnosis should be carefully made together with clinical examinations and detailed familial studies even in cases of suspected HoFH where the mutations detected are apparently in 0 alleles or only 1 allele, because a genetic test does not exclude the possibility of HoFH due to unknown gene mutations. Consultation with experienced specialists is required in such cases.

6. Screening/Follow-Up for ASCVD

Most HoFH patients may die of ASCVD before 30 years old if untreated^{33, 34)}. Once HoFH is suspected, extensive examination for ASCVD should be carried out. In HoFH, the potentially fatal disorders of angina pectoris, myocardial infarction, and aortic supra-valvular and valvular stenosis could occur even in childhood (**Fig. 2**). Aortic supra-valvular and valvular stenosis in HoFH is sometimes difficult to treat and lethal³⁵⁾. If patients are left untreated until around 20 years old, ASCVD risk is extremely high. Heart and aortic disease proceeds and systemic atherosclerosis develops later in life.

Non-invasive tests such as cardiac ultrasonography, carotid ultrasonography, and electrocardiograms should be conducted first, and enhanced CT for the aorta and coronary artery and coronary angiography should be considered when necessary³⁶⁾. Exercise stress tests should be carefully performed with consideration for patient safety.

7. Differential Diagnosis

A differential diagnosis should be made using

high LDL-C levels and prominent xanthomas. LDL-C may be elevated to HoFH levels by secondary hypercholesterolemia such as hypothyroidism or nephrotic syndrome. Xanthomas may develop due to hypercholesterolemia in primary biliary cholangitis. Sitosterolemia, caused by the ATP-binding cassette transporter ABCG5/ABCG8 gene (*ABCG5/ABCG8*) mutations³⁷⁾, sometimes exhibits elevation of LDL-C and skin xanthomas comparable to HoFH during the suckling stage³⁸⁾. Although LDL-C elevation and skin xanthomas subside after weaning from breastfeeding, elevated levels of plasma plant-sterols (including sitosterol) persist in these patients. There is also cerebrotendinous xanthomatosis (CTX), an autosomal recessive disease caused by sterol 27-hydroxylase gene (*CYP27A*) mutations, which is characterized by prominent xanthomatosis in the tendon and brain and sometimes accompanied by central nervous symptoms (mental retardation, cognitive impairment, or motor ataxia)³⁹⁾. CTX is clinically diagnosed by elevated plasma cholestanol levels. A differential diagnosis should be carefully made because these diseases require specific therapeutic approaches.

8. Treatment of HoFH

HoFH patients may suffer fatal ASCVD from infancy so initiation of aggressive LDL-C lowering as early as possible is essential for preventing their premature deaths^{1, 4)} (**Fig. 3**, **Fig. 4**). Specific therapeutic strategies for preventing ASCVD development in individual cases should be planned in addition to LDL lowering.

Patients as well as their families will be burdened by various sources of stress such as anxiety about prognosis, concern about heredity, and costs of treatments. Supportive information should be provided, including that on possible financial aid, the therapeutic options available, and genetic counseling. Financial aid is available under The Program for Designated Intractable Diseases of the Japanese public healthcare system. Pediatric FH patients can receive support separately under The Program of Medical Aid for Chronic Pediatric Diseases of Specified Categories, which covers both HeFH and HoFH. In practice, consultation with specialists should strongly be advised.

1) Adult HoFH (15 years of age or older)

The LDL-C management goal is less than 100 mg/dL in primary prevention, and less than 70 mg/dL in secondary prevention¹⁾ in the Japanese guideline (**Fig. 3**). Medication should start with statins at appropriate doses⁴⁰⁾, followed by increasing them to maximal tolerated doses and combination with other

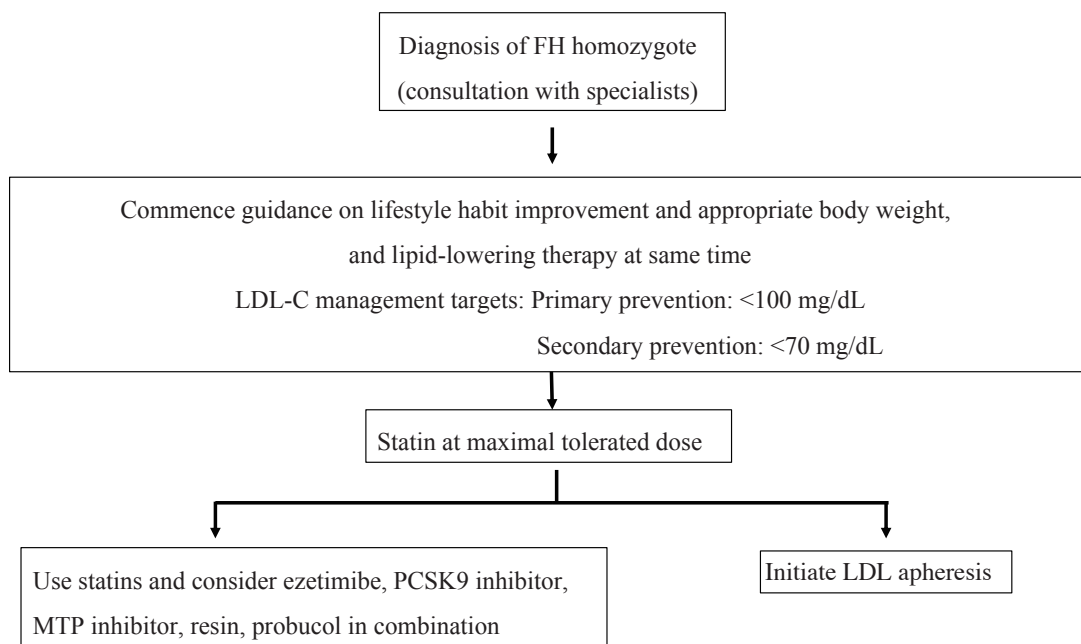


Fig. 3. Algorithm for treatment of adult (15 years of age or older) FH homozygotes

In HoFH, powerful LDL-C lowering therapy is required from a young age to prevent the onset and progression of CAD. Combination of lipid-lowering drugs, including MTP inhibitor, and lipoprotein apheresis is required in many patients with HoFH. (Adapted from Guidelines for Diagnosis and Treatment of Familial Hypercholesterolemia 2017) “LDL apheresis” means “lipoprotein apheresis” in this review)

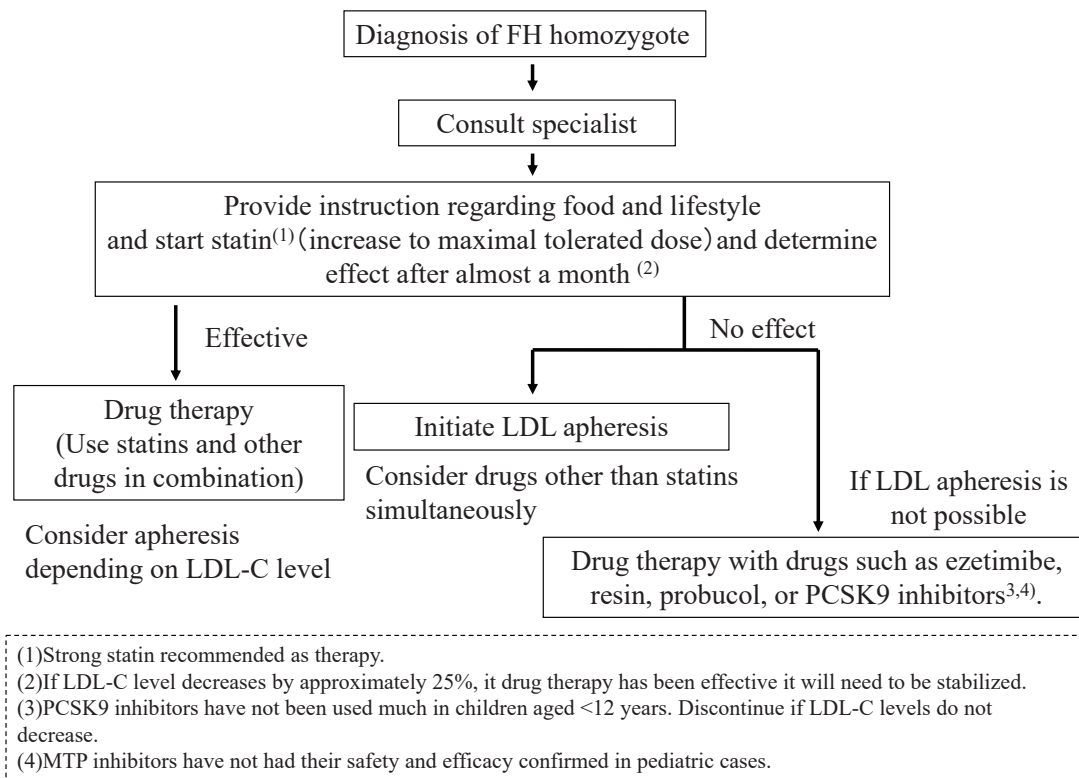


Fig. 4. Algorithm for treatment of pediatric FH homozygotes

Lifestyle interventions and maximally tolerated statin therapy should be started at the initial diagnosis. Since LDL-C targets are rarely achieved, lipoprotein apheresis therapy is recommended, and should be commenced by age 5 ideally.

drugs⁴¹⁻⁴³). Achievement of these goals with drug treatment only is, however, not easy in HoFH.

Statins, ezetimibe and PCSK9 inhibitors all act by enhancing LDL receptor activity^{44, 45}), so their effectiveness depends on residual LDL receptor activity in the individual HoFH patient. Many HoFH patients are refractory to these drugs. However, if any of them are effective in lowering LDL-C, they should be continued together with the additional treatments described below.

MTP inhibitors (lomitapide) are a class of oral drug that is independent of LDL receptor activity. Clinically, they are indicated only for HoFH, and a decrease in LDL-C to approximately half of the pretreatment level can be achieved in many HoFH cases, if tolerated⁴⁶⁻⁴⁹). The main adverse effects are gastrointestinal symptoms and liver enzyme elevation accompanied by fat accumulation, similar to the symptoms observed in patients with MTP deficiency⁵⁰). The MTP inhibitor should be started with the lowest dose, taking adequate measures in accordance with nutritional guidance (restricted fat and alcohol intake), and then the dose should be carefully increased gradually.

Lipoprotein apheresis directly removes LDL from plasma through selective absorption or filtration of LDL using an extra-corporal circulation system, and this has been the core therapy for HoFH to date⁵¹⁻⁵³). LDL-C levels can be precisely decreased by this procedure, depending upon the treated plasma volume, when properly performed. Lipoprotein apheresis not only removes LDL but also has potential pleiotropic effects in preventing atherosclerosis through removal of cell adhesion molecules⁵⁴, coagulation factors⁵⁵, and inflammatory cytokines⁵⁶. Lipoprotein apheresis for HoFH once every 1 to 2 weeks is covered by Japanese public healthcare insurance. The use of ACE inhibitors is contraindicated for patients treated by lipoprotein apheresis with the Liposorber system and selective absorption of LDL by dextran sulfate-cellulose because shock may occur due to an increase in bradykinin activation.

Another option is liver transplantation. While this is highly invasive, it has been shown to be a feasible therapeutic option for reversing atherosclerotic changes in HoFH patients that are uncontrollable with conservative therapy^{57, 58}).

2) Pediatric HoFH

Even in the suckling stage, children with HoFH must be referred to specialists for initiation of lipid-lowering therapy, as this is the key to a better prognosis⁴). The target LDL-C level should be the same as for adult HoFH in secondary prevention

(though not clearly stated in the current pediatric guideline⁴). In pediatric HeFH, it is set at less than 140 mg/dL for primary prevention.

Statins and life-style interventions must be started at the time of diagnosis. Statins must be up-titrated and efficacy should be evaluated within a 1-month interval in order to titrate up to the maximal tolerated doses. Combination therapy with ezetimibe, bile sequestering resins, and PCSK9 inhibitors should be considered. These strategies may be effective in cases where there is a response in residual LDL receptor activity. Probucol should also be considered as it could reduce LDL in HoFH due to an unknown mechanism. Administration of an MTP inhibitor could be considered but only with extreme caution because no results of clinical trials in children have been reported. Drug therapy should be conducted until it becomes possible to commence lipoprotein apheresis.

In any case, lipoprotein apheresis must be considered since LDL-C targets are seldom achieved in HoFH only with drug treatment. This extracorporeal circulation therapy is generally commenced at the age of 5 or older, though it has reportedly been started in a patient who was 3.5 years old. In Japan, the main method is selective LDL absorption by dextran sulfate cellulose. However, with the aim of reducing extracorporeal volume, simple plasma exchange can be selected for children with a bodyweight under 30 kg.

3) Treatment during Pregnancy in HoFH

Female HoFH patients could be treated in the same way as for secondary prevention on reaching childbearing age. During pregnancy, LDL and VLDL are generally increased, and continuation of LDL-lowering therapy would be important. Statins and many other drugs are contraindicated during pregnancy and breastfeeding, and only bile sequestering resins can be used, taking proper care, but their LDL-lowering effects are limited⁵⁹). It has been reported that lipoprotein apheresis is effective and feasible during pregnancy, and a case of cardiovascular death caused by suspension of apheresis during pregnancy⁶⁰) has been reported. Consultation with experienced specialists is recommended for pregnancy in HoFH.

Future Perspectives

Therapeutic options are still limited for HoFH, and all-out efforts should be made to achieve the best combination of feasible therapies in many cases. However, each therapeutic strategy has its advantages

and disadvantages so new therapies are awaited.

Inclisiran, a new siRNA drug that inhibits translation of PCSK9, is being developed⁶¹. As the effect of one injection lasts 6 months to 1 year, this drug may be a good option for HoFH patients who respond to PCSK9 inhibitors. Inclisiran was approved in the European Union in December 2020.

Evinacumab, an anti-ANGPTL3 antibody, is a new class of drug that is reportedly effective even in HoFH⁶², and clinical trials are ongoing in Japan and other countries⁶³. The LDL-C lowering effect of evinacumab is independent of LDL receptor activity.

Mipomersen (Kynamro), an antisense drug for the *APOB* gene, has moderate LDL-lowering effects but has the adverse effects of liver damage and injection site reactions. It was approved by the FDA for HoFH in 2013⁶⁴ but rejected by the European Medicines Agency, and FDA approval was eventually withdrawn in 2019.

Gene therapy for HoFH has been investigated, but is still in the experimental stage. Since HoFH is a relatively rare disease, even if approved, demand for therapies would not be very high anywhere in the world. Lomitapide had been approved only for the treatment of HoFH in just 38 countries as of March 2021, including those in North and South America, the European Economic Area, and only Japan in East Asia. Lipoprotein-apheresis, which requires specific equipment, is available in a limited number of countries. Wider availability of therapeutic measures for HoFH should encourage its more active diagnosis worldwide.

Early diagnosis of FH is essential for preventing premature death in patients, whether they are hetero- or homozygotes⁶⁵⁻⁶⁷. Universal screening of plasma lipid levels during childhood has been trialed in some parts of Japan and we expect that such trials on local universal screening will lead to a nationwide system. In addition, reverse cascade screening, in which family members are screened on the basis of child probands, and continued worldwide registry research should improve the effectiveness of finding FH⁶⁸⁻⁷⁶.

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Conflicts of Interest

Atsushi Nohara has nothing to disclose. Hayato Tada has nothing to disclose. Masatsune Ogura has

received honoraria from Amgen Inc., Astellas Pharma Inc. Sachiko Okazaki has received scholarship grants from Minophagen Pharmaceutical Co., Ltd., Kowa Company, Ltd. Koh Ono has nothing to disclose. Hitoshi Shimano has nothing to disclose. Hiroyuki Daida has received honoraria from Amgen Inc., Daiichi-Sankyo Co., Ltd., Kowa Co., Ltd., and MSD K.K., Novartis Pharma K.K., Bayer Yakuhin, Ltd. and received clinical research funding from Canon Medical Systems Corporation, Philips Japan, Ltd., Toho Holdings Co., Ltd., Asahi Kasei Corporation, and Inter Reha Co., Ltd. HD has also received scholarship grants from Nippon Boehringer Ingelheim Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Sanofi K.K., MSD K.K., Daiichi-Sankyo Co., Ltd., Pfizer Co., Ltd., Mitsubishi Tanabe Pharma Corp., Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Teijin Pharma, Ltd., Shionogi & Co., Ltd., Actelion Pharmaceuticals, Ltd., Actelion Ltd., Kowa Co., Ltd., Bayer Yakuhin, Ltd. HD has also courses endowed by companies, including Philips Japan, Ltd., ResMed, Fukuda Denshi Co., Ltd., and Paramount Bed Co., Ltd. Kazushige Dobashi has nothing to disclose. Toshio Hayashi has nothing to disclose. Mika Hori has nothing to disclose. Kota Matsuki has nothing to disclose. Tetsuo Minamino has nothing to disclose. Shinji Yokoyama has nothing to disclose. Mariko Harada-Shiba has received stock holdings or options from Liid Pharma, honoraria from Amgen Inc., Astellas Pharma Inc., Sanofi, and scholarship grants from Aegerion Pharmaceuticals, Inc., Recordati Rare Diseases Japan, and Kaneka Corporation. Katsunori Ikewaki has nothing to disclose. Yasushi Ishigaki has nothing to disclose. Shun Ishibashi has received honoraria from Kowa Co., Ltd., and a scholarship grant from Ono Pharmaceutical Co., Ltd. Kyoko Inagaki has nothing to disclose. Hirotohi Ohmura has nothing to disclose. Hiroaki Okazaki has received scholarship grants from Minophagen Pharmaceutical Co., Ltd., Kowa Company, Ltd. Masa-aki Kawashiri has nothing to disclose. Masayuki Kuroda has nothing to disclose. Masahiro Koseki has received clinical research funding from Kowa Company, Ltd., Rohto Pharmaceutical Co., Ltd. Takanari Gotoda has nothing to disclose. Shingo Koyama has nothing to disclose. Yoshiki Sekijima has nothing to disclose. Manabu Takahashi has nothing to disclose. Yasuo Takeuchi has nothing to disclose. Misa Takegami has nothing to disclose. Kazuhisa Tsukamoto has received honoraria from Bayer Yakuhin, Ltd., MSD Ltd., Takeda Pharmaceutical Company Ltd., and scholarship grants from Mitsubishi Tanabe Pharma Corporation., Bayer Yakuhin, Ltd., Sanofi K.K. Atsuko Nakatsuka has nothing to disclose. Kimitoshi

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