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Guidance for Pediatric Familial Hypercholesterolemia 2017

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Joint Working Group by Japan Pediatric Society and Japan Atherosclerosis Society for Making Guidance of Pediatric Familial Hypercholesterolemia

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This paper describes consensus statement by Joint Working Group by Japan Pediatric Society and Japan Atherosclerosis Society for Making Guidance of Pediatric Familial Hypercholesterolemia (FH) in order to improve prognosis of FH.

FH is a common genetic disease caused by mutations in genes related to low density lipoprotein (LDL) receptor pathway. Because patients with FH have high LDL cholesterol (LDL-C) levels from the birth, atherosclerosis begins and develops during childhood which determines the prognosis. Therefore, in order to reduce their lifetime risk for cardiovascular disease, patients with FH need to be diagnosed as early as possible and appropriate treatment should be started.

Diagnosis of pediatric heterozygous FH patients is made by LDL-C ≥ 140 mg/dL, and family history of FH or premature CAD. When the diagnosis is made, they need to improve their lifestyle including diet and exercise which sometimes are not enough to reduce LDL-C levels. For pediatric FH aged ≥ 10 years, pharmacotherapy needs to be considered if the LDL-C level is persistently above 180 mg/dL. Statins are the first line drugs starting from the lowest dose and are increased if necessary. The target LDL-C level should ideally be < 140 mg/dL. Assessment of atherosclerosis is mainly performed by noninvasive methods such as ultrasound.

For homozygous FH patients, the diagnosis is made by existence of skin xanthomas or tendon xanthomas from infancy, and untreated LDL-C levels are approximately twice those of heterozygous FH parents. The responsiveness to pharmacotherapy should be ascertained promptly and if the effect of treatment is not enough, LDL apheresis needs to be immediately initiated.

Key words: Pediatric familial hypercholesterolemia, Homozygote, Heterozygote, Diagnostic criteria, Guidance, Lifestyle, Pharmacological therapy, LDL apheresis

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Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant hereditary disease in which mutations occur in the low-density lipoprotein (LDL) receptor and its related genes[1)]. Historically, the frequency of homozygous FH (HoFH) used to be estimated as 1 in 1,000,000, and that of heterozygous FH (HeFH) as 1

Table 1. Pediatric FH diagnostic criteria

1. Hyper-LDL cholesterolemia: LDL-C level of ≥ 140 mg/dL when untreated (If total cholesterol level is ≥ 220 mg/dL, measure the LDL-C level) 2. Family history of FH or premature CAD (blood relative closer than the two parents)
• Excluding secondary hyperlipidemia, if two items are satisfied, FH is diagnosed. • During the growth phase, there are fluctuations in LDL-C; therefore, careful observation is required. • In pediatric cases, there are few clinical symptoms such as xanthomatosis; therefore, it is important to investigate the family history for FH. Use the family survey results of those beyond the parents as a reference if necessary. • Early CAD is defined as CAD with an onset at < 55 years of age for males and < 65 years of age in females, respectively • If xanthoma is present, LDL-C is suspected to be extremely high (homozygote).

in 500. However, a recent study in Japan suggested that the prevalence of HeFH might be as high as 1 in 200[2]. Accordingly, HoFH may be present in as many as 1 in 160,000 people and this indicates that HeFH may be present in 1 in 200-500 of the general population. Unfortunately, FH is underdiagnosed.

FH is characterized by life-long elevated plasma LDL cholesterol (LDL-C) levels, presence of tendon xanthomas, and increased risk of premature atherosclerotic cardiovascular disease (ASCVD). With sustained exposure of the arterial wall to elevated LDL-C levels, atherosclerosis develops, especially in the coronary arteries. In this regard, both the Bogalusa Heart Study[3] (pre-mortem study) and the Pathobiological Determinants of Atherosclerosis in Youth Study[4] (post-mortem study) have clearly shown an association between atherogenic lipoprotein levels and atherosclerosis, even in children. Therefore, early diagnosis and optimal treatment from childhood are critical in preventing premature ASCVD in children and adolescents with FH.

The purpose of this consensus paper is to improve early diagnosis and provide optimal treatment for FH from childhood in Japan. We provide guidance on its diagnosis and screening, evaluation of atherosclerosis, and management of children and adolescents with FH. The guidelines provided were jointly developed by the Japan Pediatric Society and the Japan Atherosclerosis Society.

1. Diagnosis of Pediatric HeFH

Key Points

• Family history (e.g. in parents, grandparents, and siblings) of FH as well as premature CAD is important in diagnosing pediatric FH.

• Since plasma LDL-C levels fluctuate during childhood, LDL-C levels should be measured multiple times.

• After diagnosis of FH, a family survey should be conducted to find others with FH in the patient's family (cascade screening or family screening, hereafter cascade screening).

Importance of Early Detection of FH

Hypercholesterolemia is present in pediatric HeFH from birth but CAD-related symptoms, such as angina, are rarely observed during childhood. Therefore, in most cases, hypercholesterolemia is unexpectedly detected when blood tests are performed. In HeFH patients, ASCVD typically occurs in middle age or at an older age; however, a previous study reported that atherosclerosis rapidly progresses at an age of around 10 years, and statin treatment can delay its progression[5]. Based on the results of this study, early diagnosis of FH and initiation of statin treatment during childhood have been considered necessary for preventing the onset of ASCVD in Europe and America, where guidelines for diagnosis and treatment of pediatric FH have been drawn up, and aggressive treatments are recommended[6].

Diagnostic Criteria for pediatric FH

Diagnostic criteria for pediatrid HeFH in Japan were defined by the Japan Atherosclerosis Society in 2012[7]. As FH is an autosomal dominant hereditary disorder, asking about family history is very important for diagnosis. The diagnostic criteria for pediatric FH (**Table 1**) in this treatment guide are essentially the same as those established by the Society. However, as these criteria enable not only HeFH but also HoFH to be diagnosed, the title of the criteria was amended. In addition to the definition of high LDL-C levels for FH (≥ 140 mg/dL), the Society's 2012 guidelines include the criterion of TC ≥ 220 mg/dL, the 95th percentile of TC in the pediatric clinical setting. Blood tests should be conducted in the fasting state and LDL-C levels should be calculated using Friedewald's Formula.

Fig. 1 gives an algorithm for the diagnosis of pediatric FH. If an individual fulfills both diagnostic criteria 1 and 2, i.e. LDL-C level of ≥ 140 mg/dL, and family history within second-degree relatives (FH or

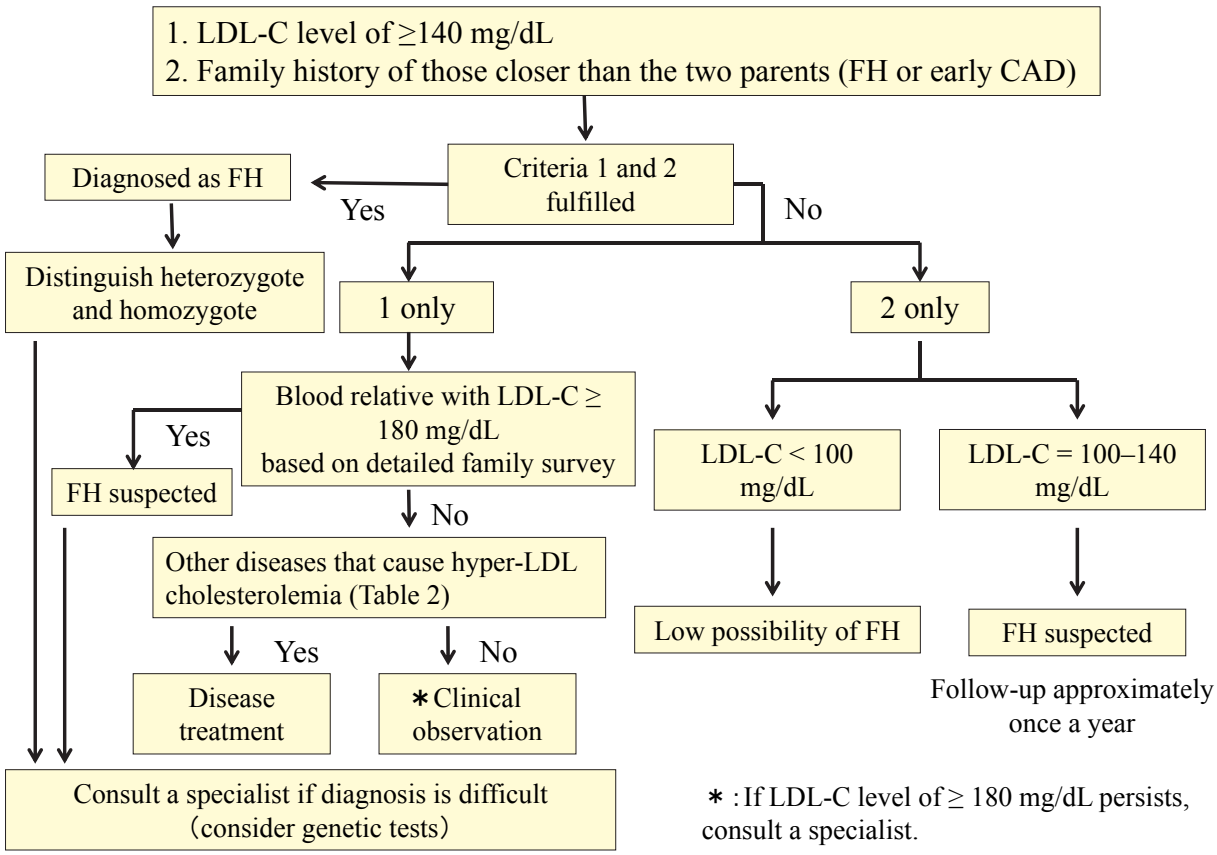

Fig. 1. Algorithm for diagnosing pediatric FH

premature CAD), a diagnosis of FH is made. Secondary hyperlipidemia should be ruled out if only criterion 1 is met. Although hypercholesterolemia is often caused by overweight, it is noteworthy that no significant association was observed between body weight and an LDL-C level of ≥140 mg/dL[8]. Therefore, if a child has an LDL-C level of ≥140 mg/dL and is obese, FH should be suspected. In this case, genetic testing is also recommended. When family history is absent, it is important to rule out hypercholesterolemia due to other diseases as shown in **Table 2**.

Plasma LDL-C levels vary even with the same genetic mutations in the LDL receptor[9-11]. As they fluctuate greatly during childhood, blood tests should be performed repeatedly if the child meets only criterion 2 (every 3 to 6 months). The child will be diagnosed with FH if LDL-C levels of ≥140 mg/dL are observed more than once. It is unlikely that FH will be diagnosed if the child has low levels of LDL-C less than 100 mg/dL. If the LDL-C level is between 100 and 140 mg/dL, follow-up over a few years (at least annual LDL-C measurement) is necessary.

Screening for Pediatric FH

Historically, universal screening was conducted during the 1990s in Kumamoto City, and many infants were consequently diagnosed as HeFH[12]. However, from the viewpoint of medical economics, cascade screening is considered to be a more realistic means of finding FH than universal screening. The diagnosis rate of FH in both children and adults will exponentially increase if cascade screening is carried out more. Financial assistance is available for pediatric HeFH under a grant-in-aid program for chronic diseases in childhood.

In conducting cascade screening it needs to be kept in mind that FH is basically an autosomal dominant disease[13]. If a mother or father has HeFH, there is a 50% probability that the child will also have HeFH. If both parents have HeFH, then the child has a 25% probability of having HoFH and a 50% chance of having HeFH. Since ASCVD can be prevented by early diagnosis and optimal treatment of FH, it is recommended that cascade screening and blood tests are performed by the age of 10 (or earlier for HoFH). Principles of genetic counseling for FH in consideration of its autosomal dominant nature are described

Table 2. Differential diagnosis of hyper-LDL cholesterolemia

Hereditary diseases		
Disease name	Cause	Identifying points
Sitosterolemia	ATP-binding cassette transporter G5, G8 gene (*ABCG5*, *ABCG8*) abnormality	Autosomal recessive inheritance Raised serum sitosterol LDL-C not very high despite the xanthoma. Hyper-LDL cholesterolemia can be shown at FH homozygote level during infancy temporarily.
Cerebrotendinous xanthomatosis (27-hydroxylase deficiency)	Sterol 27-hydroxylase gene (*CYP27A1*) abnormality	Autosomal recessive inheritance, progressive neurological disorders Raised serum cholestanol Cholesterol is not high but xanthoma is evident Accumulates in the brain too.
Wolman disease Cholesteryl ester storage disease (lysosomal acid lipase deficiency)	Lysosomal acid lipase gene (*LIPA*) abnormality	Autosomal recessive inheritance Hepatomegaly Typically, there is notable hepatosplenomegaly and liver damage due to fatty liver or liver sclerosis but the severity can vary and there are cases which are not diagnosed until adulthood. In adults it often leads to hyper-LDL cholesterolemia.
Secondary diseases		
• Nephrotic syndrome • Hypothyroidism • Diabetes • Cholangiolithic hepatitis		• Obesity • Anorexia nervosa • Diet related (excessive intake of dairy products) • Drug-induced (steroids, cyclosporin, etc.)

in the supplementary materials.

2. Diagnosis of Pediatric HoFH

Key Points

• Skin xanthomas or tendon xanthomas from infancy, and untreated LDL-C levels are approximately twice those of HeFH parents

• Two pathogenic mutants in FH causative genes

Clinical Features of Pediatric HoFH

Pediatric HoFH, as a general rule, involves the inheritance of FH causative genetic mutations from each parent and is diagnosed from serum LDL-C levels being approximately twice those of a patient's HeFH parents or other HeFH family members. When untreated, the LDL-C level is usually ≥500 mg/dL; and if the level is ≥400 mg/dL, HoFH should be suspected. It is important to check the parents or family members of a patient for clinical features, such as serum LDL-C levels, tendon xanthomas, and premature CAD, as well as possible consanguinity. With HoFH, the frequent appearance of skin xanthomas in flexures during infancy, usually those of the wrist and ankles, is often the chief complaint when visiting clinics. Other findings that suggest HoFH are xanthoma tuberosum, xanthomas in webbing of fingers and those in the buttocks. These xanthomas can be improved by LDL-C reduction therapy. Tendon xanthomas in HoFH are not generally apparent during infancy but appear at an earlier stage than those in HeFH and are more prominent.

Genetic Diagnosis of HoFH

Two pathogenic mutant alleles in FH causative genes give a definite genetic diagnosis. Among FH causative genes, *LDLR* codes the LDL receptor, *APOB* codes the apolipoprotein B-100, *PCSK9* codes proprotein convertase subtilisin/kexin type 9 (PCSK9), and *STAP1*, another recently reported gene, codes signal transducing adaptor family member 1[14]. Only one pathogenic mutation from parents means HeFH, and two pathogenic mutations means HoFH in genetic diagnosis. Nearly all FH is caused by genetic mutations in *LDLR*; however, in Japan, approximately 5% of HeFH is caused by a gain-of-function mutation of

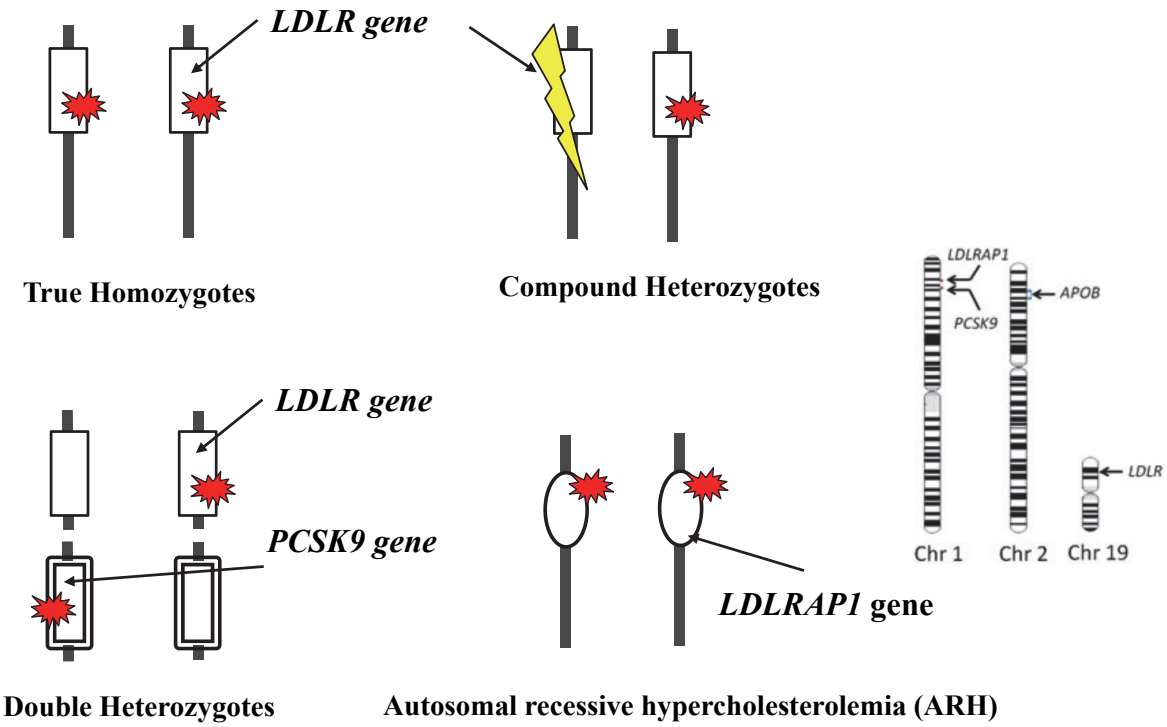

Fig. 2. Combination of genetic mutation showing FH homozygote clinically

PCSK9. FH due to *APOB* is common among Western populations but has not been reported in the Japanese population.

Autosomal recessive hypercholesterolemia (ARH) is an autosomal recessive disorder that is caused by mutations in LDL receptor adaptor protein 1 (LDLRAP1) genes. While homozygotes for *LDLRAP1* mutations manifest the clinical HoFH phenotype, heterozygotes for these mutations do not have high LDL-C levels, unlike heterozygotes for *LDLR* mutations. ARH is extremely rare, and only a few cases have been reported in Japan[15, 16].

HoFH may be distinguished on the basis of the genetic diagnosis (**Fig. 2**). Autosomal genes are inherited from the father and mother, and if it is the same mutation in the same gene, this is a true homozygote; if it is a combination of different mutations in the same gene, this is a compound heterozygote; and if it is a combination of mutations in different genes, this is a double heterozygote. In Japan, the clinical features of double heterozygotes for *LDLR* and *PCSK9* gain-of-function mutations have been reported. However, their symptoms are relatively mild and their response to statins and other drug therapies is maintained as compared to true homozygotes or compound heterozygotes for *LDLR* mutations[17, 18]. The receptor-defective type of *LDLR* mutation produces milder phenotypes than the receptor-negative type.

As responses to lipid-lowering treatments will differ depending on the genetic mutations, genetic diagnosis should be performed if HoFH is suspected. One should keep in mind that there are cases where phenotypic inheritance does not follow simple Mendelian inheritance in the case of a double heterozygote. For example, HoFH phenotypes can be inherited from one parent with HoFH. Conversely, children from clinically HoFH parents may have normal LDL-C levels.

Important Notes for Diagnosis of HoFH

There are variations in the clinical phenotypes for HoFH, and HoFH may be genetically diagnosed even when patients have an LDL-C level < 500 mg/dL.

HoFH is accompanied by the rapid progression of ASCVD, such as CAD or aortic disease such as supra-aortic stenosis (**Supplementary Fig. 1**), from infancy, and the prognosis is extremely unfavorable, with early deaths from infancy. Furthermore, skin xanthomas are observed in almost all cases of HoFH (**Supplementary Fig. 2**).

If HoFH is suspected because skin xanthomas or marked tendon xanthomas are observed, or the LDL-C level is high for HeFH, a consultation with specialists from the Japan Atherosclerosis Society is essential to make decisions regarding the diagnosis and the treatment plan.

In Japan, the guardians of pediatric HoFH patients can apply for financial support under Medical Aid for Chronic Pediatric Diseases of Specified Categories as well as under the category of Designated Intractable Diseases covered under the Japanese National Health Insurance system.

Differential Diagnosis

If a HeFH phenotype is not present in either of a patient's parents, conditions such as ARH should be suspected. Furthermore, in the case of sitosterolemia (high serum plant sterol levels) and that of cerebrotendinous xanthomatosis (high serum cholestanol levels), prominent xanthomas should be found (**Table 2**). Sitosterolemia has particularly marked fluctuation in cholesterol levels, and in some cases, LDL-C levels are comparable with those of HoFH during breast feeding. Skin xanthomas may be present during infancy[19].

3. Evaluation for Atherosclerotic Cardiovascular Diseases in Pediatric FH

Key Points

- If Achilles tendon thickening or atherosclerosis of carotid arteries is observed in pediatric patients with HeFH, regular examination for CAD is desirable.
- Since atherosclerotic lesions can progress at the early stage in pediatric patients with HoFH, regular, systemic examination for ASCVD by specialists is required. Examination for presence of frequently occurring CAD, aortic valve stenosis and supravalvular aortic stenosis, and thoracic/abdominal aortic aneurysms is particularly recommended.
- To avoid radiation exposure in children as much as possible, non-invasive examination by ultrasonography (e.g. carotid ultrasonography, transthoracic echocardiography, and abdominal ultrasonography) is preferable.
- If necessary, screening for CAD can be conducted by coronary artery computed tomography (CT). If significant stenosis is suspected, the patient should be hospitalized for coronary angiography (CAG).

HeFH

With HeFH, the incidence of CAD is low during childhood. However, since atherosclerotic lesions may progress more rapidly in HeFH children than in healthy children, examinations should be performed when necessary, mainly by non-invasive means. If thickening and/or atherosclerotic plaques are observed in carotid ultrasonography or when the Achilles tendon is thick, atherosclerotic disease should be suspected, and regular examinations would be desirable.

HoFH

1) Medical Questionnaire

Ischemic symptoms of CAD may occur even during childhood, so a medical questionnaire should be administered, with questions to determine if there is any chest pain, frontal chest tightness, or radiating pain in the neck and left hand during exertion and whether these symptoms lessen following rest. For peripheral arterial disease (PAD), patients should be questioned concerning pain in the lower extremities when walking (intermittent claudication) and whether this is alleviated in the resting state. Regarding aortic valve stenosis or supravalvular aortic stenosis, they should be asked whether there is any shortness of breath upon exertion.

2) Physical Findings

There are few physical findings relating to CAD in childhood. However, for PAD, presence of arterial pulsation and attenuation can be confirmed, in which case the femoral, popliteal, and dorsal arteries in the lower extremities are palpated, blood pressures in the upper and lower extremities are measured and the ratio between them [ankle−brachial index (ABI)] is calculated. When aortic valve systolic murmurs are heard in auscultation, aortic valve stenosis or supravalvular aortic stenosis is suspected, and vascular murmurs in the lower extremity arteries may suggest the presence of arterial stenosis.

3) Biochemical Examination

In the case of acute myocardial infarction, serum CK-MB and troponin T levels would be elevated.

4) Morphological Examinations

Noninvasive Examinations

Exercise electrocardiogram: An exercise electrocardiogram using a treadmill is useful. However, as patients can be exercise test-positive due to supravalvular aortic stenosis, exercise electrocardiography should be performed after examining for the presence of aortic valve stenosis or supravalvular aortic stenosis with transthoracic echocardiography, which is described below. We should also consider the risk of ventricular fibrillation occurring due to induced myocardial ischemia.

Ultrasound: This exam is effective for assessing the degree of atherosclerosis in the peripheral arteries, particularly the carotid artery, examining for the presence of plaques and changes in intima−media thickness (IMT) and for evaluating long-term rates of change.

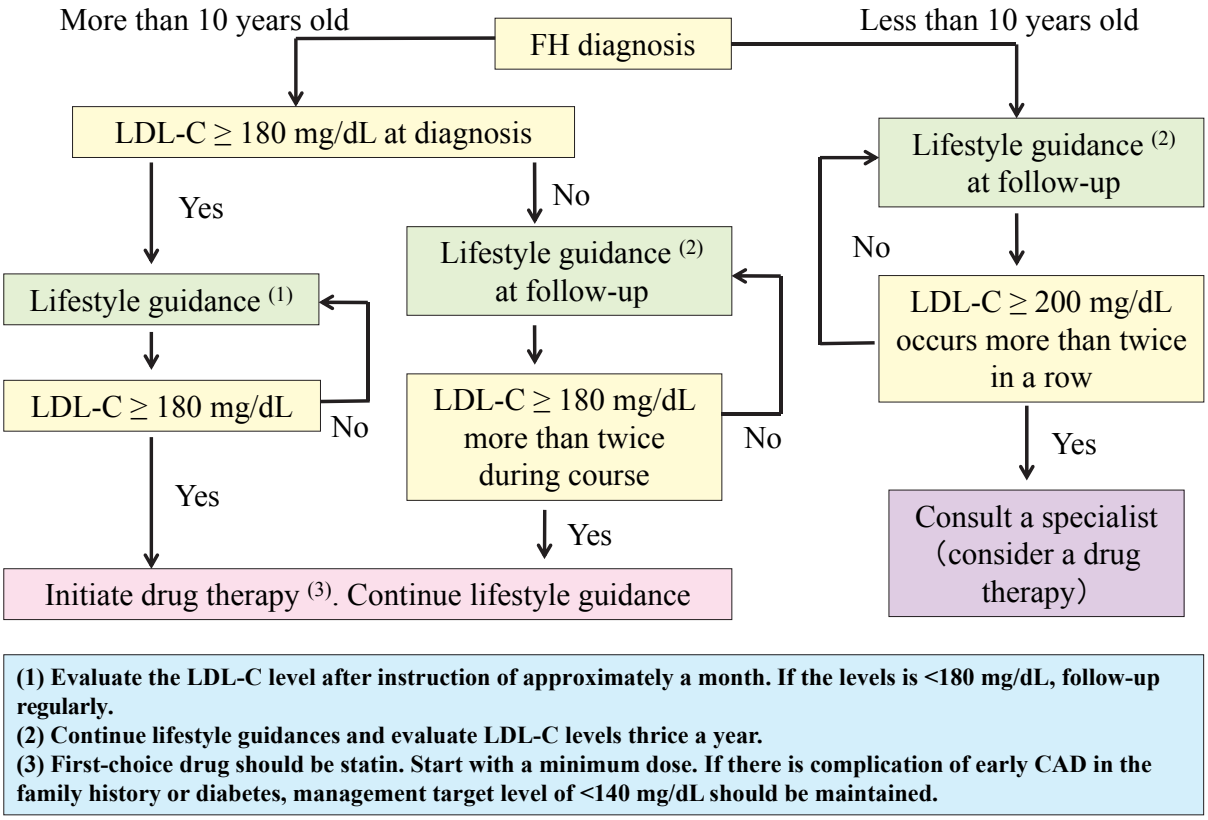

Fig. 3. Algorithm for treatment of pediatric FH heterozygote

Diagnoses of aortic valve stenosis and supravalvular aortic stenosis and evaluations of heart function are performed using transthoracic echocardiography.

CT: In pediatric HoFH, cerebrovascular lesions are rare, and evaluations focus on the coronary artery. Coronary artery CT may result in exposure to a high dose of radiation, and therefore should be conducted in children only if really necessary.

Magnetic resonance imaging (MRI) and MR angiography (MRA): These modalities enable examination for stenotic lesions in the aorta, peripheral artery, and coronary artery. In CT and MRI examinations, if procedural sedation is required due to the patient's age, attention should be paid to safety in order to prevent accidental complications.

Invasive Examinations

If progression of atherosclerosis is suspected, the extent of vessel lumen stenosis can be evaluated using angiography, but the level of radiation exposure should be minimized in childhood. If CAD is suspected, the patient should be hospitalized and CAG and left ventricular and aortic angiography should be performed.

4. Treatment of Pediatric FH

When FH is diagnosed, patients should be provided with guidance regarding lifestyle habits as quickly as possible in order to reduce the risk for atherosclerosis. This should include efforts to reduce LDL-C levels. When the effect of improving lifestyle habits is insufficient, drug therapy should be considered, initiating it from the age of 10. For pediatric HoFH, a specialist should be consulted, and if the response to drug therapy is insufficient, liopoprotein apheresis should be promptly initiated.

(1) Guidance on Lifestyle Habits

Key Points

• Provide guidance regarding lifestyle habits, including that on diet, at an early stage. This guidance should be continued after initiating drug therapy.

• Dietary considerations: Total calorific intake is the quantity of food required according to the age. The breakdown of energy sources should be 20%−25% fats and 50−60% carbohydrates. Saturated fatty acids should account for <7% of energy, cholesterol should be kept below 200 mg/

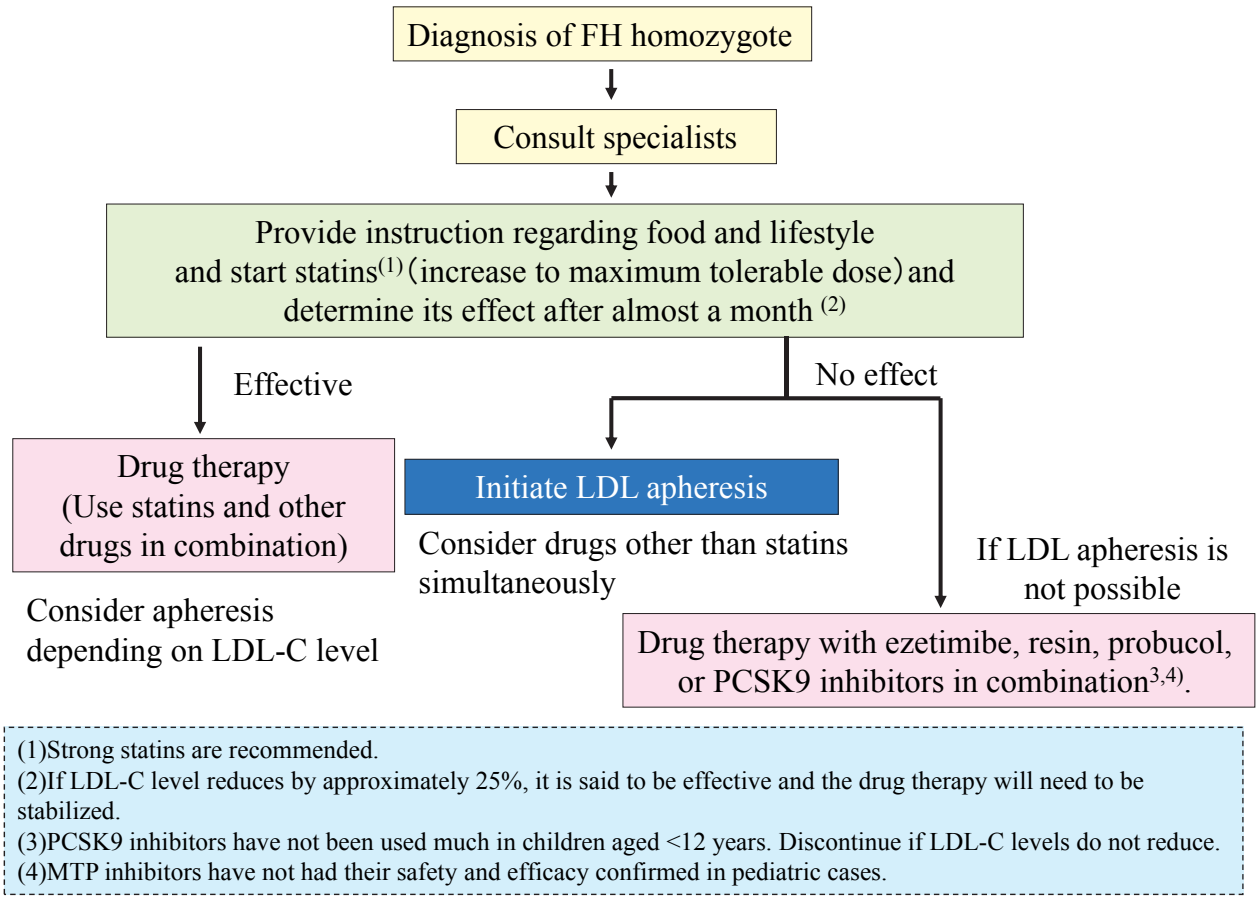

Fig. 4. Algorithm of treatment of pediatric FH homozygote
MTP: Microsomal triglyceride transfer protein

day and trans-fatty acid intake reduced. The diet should mainly comprise Japanese traditional food, with sufficient vegetable intake.

• Obesity: An appropriate weight should be maintained. With severe obesity, it is necessary to restrict energy intake. An exercise habit should be encouraged at the same time, as a good lifestyle habit.

• Exercise therapy: The patient should be helped to develop an exercise habit and maintain it.

• Prevention of smoking and passive smoking: Emphasize the point that the patient should never smoke during their lifetime. Furthermore, the cooperation of family and those around the patient should be obtained in preventing passive smoking.

Improvement in Lifestyle Habits

If FH is diagnosed, lifestyle habits, including dietary habits, should be investigated as early as possible and guidance for improving lifestyle provided[7]. This is the same approach for both HoFH and HeFH. However, even if lifestyle habits are improved, in many cases, it is difficult to keep less than 180 mg/dL of LDL-C. In such cases, drug therapy should be considered, and if the problem is serious, lipoprotein apheresis should be considered[20]. Furthermore, guidance on lifestyle habits should be continued after starting drug therapy (**Fig. 3**).

Dietary Therapy

Excluding obese children, the daily energy intake should be the normal amount for the age[21]. Food quantity and exercise level should be evaluated, and adjusted according to increases in height and weight.

Regarding nutritional balance, the guidelines for the prevention of atherosclerosis diseases[20] recommend that fat should account for 20%−25% of energy and carbohydrate 50%−60%, for patients with adult dyslipidemia. In the 2015 version of food intake standards, Dietary Reference Intakes for Japanese 2015[21], the tar-

get for energy from fat was 20%−30%, and that from carbohydrates was 50%−65%. These targets were the same from the age of 1 to 70. Thus, it is considered that pediatric diet patterns should correspond to those of adults.

There are individual differences in cholesterol absorption. In the Dietary Reference Intakes 2015[21], the scientific grounds for limiting cholesterol intake are inadequate. However, this is not considered to be applicable to patients with hyper-LDL-cholesterolemia[22]. In the Japan Atherosclerosis Society guidelines, dietary guidance for hyper-LDL-cholesterolemia states that saturated fatty acids should account for <7%, of energy and patients should reduce the intake of trans-fatty acids. Moreover, they recommend that cholesterol intake should be limited to 200 mg/day[20, 22].

Initiating strict dietary therapies in children has been found to be difficult. In recent years, the westernization of the Japanese diet has resulted in a tendency toward increased fat intake, so fats and carbohydrates should be slightly reduced in the diet. Therefore, without being too fussy about food, a traditional Japanese diet should be mainly followed and there should be a good balance of vegetables, soybean products, and fruits. Furthermore, care should be taken to prevent excessive sodium intake[20].

Prevention of Obesity

With FH, it is important to maintain an appropriate weight. Obesity, particularly that with excessive accumulation of visceral fat, can easily lead to abnormal secretion of adipocytokines in children as well as in adults[23, 24], resulting in metabolic complications and atherosclerosis. In assessing children for obesity, "percentage of overweight (POW)", a modified weight-for-height method, is used in Japan. The criterion for obesity is POW ≥20% (≥120% of the standard weight which is the age- and sex-specific weight for height), for being underweight it is POW ≤−20% (≤80% of the standard weight) for school-age children[24, 25]. For infants (≤5 years of age), a POW within ±15% is appropriate[24]. For schoolchildren, a waist circumference (navel level) of ≥80 cm is considered to strongly suggest excessive accumulation of visceral fat[24].

In obesity, because the energy intake is above the required level, returning to a normal intake is necessary. Intake of vegetables should be increased and care should be taken with regard to beverages and seasonings. During childhood, height is increasing, making it easy to reduce the obesity level (POW). However, patients should be encouraged to keep active at the same time. For advanced obesity, it is necessary to restrict energy intake.

Exercise Therapy

For patients with HoFH and serious cases of HeFH, exercise guidance should be provided after heart ultrasound examinations and CAD screening (see "Evaluation of atherosclerotic disease" for details regarding examinations). As exercise is more effective for decreasing triglyceride levels and increasing high-density lipoprotein cholesterol (HDL-C) levels than for changing LDL-C levels, it can result in preventing (or mitigating) obesity and improving insulin sensitivity[20]. Thus, sufficient guidance in exercise should be provided to obese children who do not exercise in particular.

In general, adults should perform slightly challenging aerobic exercises for 30 min/day or more, preferably every day[20]. Children should also perform roughly the same type of exercise for the same duration[25]. The type of exercise is not important; however, if possible, it should be performed outdoors. It is important that the exercise is enjoyed and continued. Care should be taken to avoid watching TV or playing video games for long periods. If problems related to heart function are present, a separate exercise program should be specified.

Prevention of Smoking and Passive Smoking

Smoking is a major independent risk factor for all patients who develop atherosclerosis, and it has been found that not smoking lowers this risk[7, 20]. In FH patients, LDL catabolism is slow and LDL is susceptible to oxidization and therefore they should be told never to smoke in their lives. Others who should be told not to smoke are the patient's family and people around the patient because it has been reported that passive smoking raises the risk of CAD and diabetes[7, 20].

(2) Pharmacotherapy for Pediatric HeFH

Key Points

- The target for LDL-C management in pediatric HeFH is a level below 140 mg/dL, and if this level is not achieved through guidance in lifestyle habits, drug therapies should be considered, from the age of 10.
- The criterion for initiating drug therapies in pediatric HeFH is the same for both boys and girls, an LDL-C level of ≥180 mg/dL, from the age of 10.
- The first choice for drug therapy is statins and they should be initiated at a low dose. Assessment of symptoms, such as muscular pain, follow-up tests of liver function, such as those measuring serum AST, ALT, CK, and lipid levels, and should be conducted after 1 month and then approximately once every 3−4 months once the stable dose has

been determined. Patients should be continuously monitored for appearance of adverse effects as well as for anything abnormal in growth and secondary sexual characteristics.

Recommendations at the Time of Initiating Drug Therapy

Even in pediatric FH, a high LDL-C level is an independent risk factor for atherosclerosis. It has been reported that IMT thickening is observed in pediatric FH[26] and many guidelines in other countries have recently stated the importance of treatment from infancy in preventing future cardiovascular events[6, 27, 28]. In pediatric HeFH, if the LDL-C level is ≥180 mg/dL even after improvement of lifestyle habits, such as through dietary and exercise therapies, drug therapy should be considered for both boy and girl patients from the age of 10[6, 27, 28]. It is important to adequately explain the importance of continuing therapy over the long-term to the guardian as well as the patient (if possible) before initiating treatment. Children aged <10 years with sustained LDL-C levels of ≥200 mg/dL should be taken to a specialist for consultation so that drug therapy can be considered, taking into account LDL-C levels, age, and family history.

Current Treatment for Pediatric FH

Statins are the first-line drugs but they should be initiated at the minimum dose. In Japan, pitavastatin was approved for use in children aged ≥10 years in June 2015. In the United States, fluvastatin is approved for use from the age of 8, whereas the other statins can be initiated from the age of 10. In Europe, rosuvastatin is approved for use from the age of 6, and the other statins can be used from the age of 10 years. In Australia, atorvastatin and rosuvastatin can be initiated from the age of 6.

If the minimum dose of statin does not decrease LDL-C levels sufficiently, the following should be considered: (i) increasing the dose, (ii) changing to a more potent statin, or (iii) adding another lipid-lowering drug. Ezetimibe and resins (anion exchange resins: cholestyramine and colestimide) have been reportedly effective in combination with statin. Ezetimibe can be used for children aged ≥10 years in the United States and Europe and resins were previously the first-line drugs in both the United States and Japan. However, they have many adverse effects, including abdominal pain, abdominal distension, and constipation. Therefore, resins have not been approved for use in infants in Europe. Additionally, the effectiveness of resins in preventing atherosclerosis remains unclear. Furthermore, as resins inhibit the absorption of folic acid and fat-soluble vitamins, regular monitoring and occasional supplementation may be necessary.

Target Levels of LDL-C

The target level of LDL-C in pediatric FH is less than 140 mg/dL (95th percentile). If there is a history of premature CAD and/or diabetes in the child's family, intensification of drug treatment may be necessary to achieve LDL-C levels below 140 mg/dL. Ezetimibe and/or resins may be required to attain the LDL-C target in some patients.

Monitoring Treatment and Adherence in Pediatric FH

Recommendations for monitoring the safety and tolerability of lipid-lowering drugs in pediatric FH are similar to those for adults. Statins should be initiated at the lowest recommended dose and up-titrated according to LDL-C lowering response and tolerability. In addition, liver aminotransferases (AST and ALT), CK, and creatinine levels should be evaluated before starting treatment, and the first evaluation after initiating statin should be performed within a month. After starting treatment, lipid levels, liver aminotransferases, and musculoskeletal symptoms should also be monitored. If musculoskeletal symptoms appear, CK levels should be monitored. As children get a lot of exercise, an increase in CK levels is often observed but it is important to determine whether the CK elevation is due to statin or not.

Furthermore, it is necessary to monitor weight and growth as well as physical and sexual development. Since it has been reported that statins increase the risk for new-onset diabetes in adults[29], fasting plasma glucose and/or glycated hemoglobin should be measured in children on high-dose statins.

Difficulty in Using Statins

To make the judgment that pediatric FH patients have statin intolerance, it is necessary to have tried several statins. Also, if possible, combinations of low dose statins, ezetimibe, and resins should be tried. Six kinds of statin are available in Japan. Optimal treatment for achieving LDL-C targets should be with the most tolerated one, which could even be non-daily, and non-statin-based lipid-lowering therapy.

Pregnancy-Related Issues

As fetal teratogenicity due to statin treatment has been reported, statins should be discontinued 3 months before conception is planned, during pregnancy, and lactation. In most patients whose treatments are initiated in early life, statin treatment can be interrupted safely during pregnancy and lactation. Therefore, clinicians should explain not only the necessity of statin

treatment but also the necessity of planned conception to young girls and their guardians in advance before starting statin treatment.

(3) Drug Therapy for Pediatric HoFH

Key Points

- For pediatric FH, lifestyle interventions and maximally tolerated statin therapy should be started at the initial diagnosis. Combination therapy with ezetimibe and other lipid-lowering drugs is often required.
- Since LDL-C targets are rarely achieved, lipoprotein apheresis therapy is recommended.
- Probucol may be effective in reducing xanthomas on the skin, but it has the adverse effect of QT prolongation.

Genetic Mutations and Effects of Drug Therapy

LDL receptor activation is the main mechanism by which statins, ezetimibe, resins, and PCSK9 inhibitors decrease LDL-C levels. Therefore, the effectiveness of these drugs depends on residual LDL receptor activity in patients. Even at the maximal dose of statins, reduction in plasma LDL-C levels is modest in most HoFH patients. However, combinations of statins with other lipid-lowering drugs, including ezetimibe, resins, PCSK9 inhibitors, and probucol, have been used effectively in HoFH who are receptor-defective (2−25% residual LDL receptor activity) and can lower LDL-C levels substantially[30]. It has been reported that statins reduce ASCVD and all cause deaths even in HoFH who are receptor-negative (<2% residual LDL receptor activity)[31]. Combination of statins and PCSK9 inhibitors is highly effective in patients with a LDL receptor mutation and a PCSK9 gain-of-function mutation (double heterozygote)[32].

Current Medical Treatment for HoFH

Decreasing the elevated LDL-C in HoFH is critical to avoiding the associated ASCVD complications. Statin should be initiated as early as possible and uptitrated to the maximal tolerated dose. The effectiveness of statin treatment should be evaluated within a month after starting administration. If it is insufficiently effective, lipoprotein apheresis should be started. At the same time, other lipid-lowering drugs (e.g., ezetimibe, resins, probucol, and PCSK9 inhibitors) should be considered (**Fig. 4**)[33]. It has been reported that the maximal dose of atorvastatin decreased LDL-C by 20% in HoFH patients who were receptor defective and undergoing lipoprotein apheresis[34]. In addition, probucol reportedly decreased both LDL-C and HDL-C levels, and was effective in reducing xanthomas on the skin[35]. Furthermore, a retrospective study in Japan, which enrolled HeFH adult patients, showed that probucol significantly reduced recurrence of cardiovascular events[36]. However, as probucol has the adverse effect of QT prolongation[37], regular electrocardiography needs to be carried out[38]. In HoFH patients who have undergone lipoprotein apheresis treatment, it has been reported that ezetimibe delays new increases in LDL-C levels after treatment[39].

There is little experience of using PCSK9 inhibitors in children under 12 years old. If LDL-C levels do not decrease, administration should be terminated and lipoprotein apheresis should be initiated immediately. In Japan, PCSK9 inhibitors are approved for use in patients who have been prescribed the maximal tolerated dose of statin.

The microsomal triglyceride transfer protein inhibitor, lomitapide, is an orally administered agent and the mechanism underlying its LDL-C lowering effect is independent of LDL receptor activation. However, abdominal pain, diarrhea, liver dysfunction and fatty liver have been reported as adverse effects of this drug and although it has been already approved for use in adult patients with HoFH in Japan, it is not approved for childhood HoFH at present[40, 41].

Lipoprotein Apheresis

Key Points

- Lipoprotein apheresis treatment should be started as soon as possible in HoFH patients when statin therapy is insufficient.
- Lipoprotein apheresis should be carried out weekly or biweekly, observing LDL-C levels before and after treatment.
- Three methods of apheresis are available: simple plasma exchange, double-membrane filtration, and selective LDL absorption.

Commencing Lipoprotein Apheresis Treatment

In many HoFH patients, target LDL-C levels cannot be achieved even at maximal dose treatments. Therefore, lipoprotein apheresis should be started as early as possible when drug therapy is insufficient, with the patient lying still on the bed during treatment. Ideally, treatment should be commenced by age 5, and a case where treatment was initiated at 3.5 years has been reported[42]. In patients with coronary artery stenosis or total coronary occlusion and aortic stenosis or supravalvular aortic stenosis, clinicians should not hesitate to start lipoprotein apheresis when response to drug treatment is poor[43], even if they are infants. Until the age that lipoprotein apheresis becomes available, regular examinations and tests as well as drug therapy

should be performed.

Method of Lipoprotein Apheresis

Lipoprotein apheresis should be carried out weekly or biweekly with monitoring of pre- and post-treatment LDL-C levels. Usually, the cubital veins of both upper limbs are used for blood access. Shunting may be carried out when vascular access is poor but caution needs to be paid as there is a high risk of occlusion when LDL-C levels are high. At present, lipoprotein apheresis treatment carried out in Japan is mainly by 3 methods: simple plasma exchange, double-membrane filtration, and selective LDL absorption. Double-membrane filtration and LDL absorption are widely used for selective removal of LDL. However, their extracorporeal circulation volume is too large for patients with the body weight less than 30 kg. In this case, simple plasma exchange may be selected.

Effects of Long-Term Lipoprotein Apheresis Treatment in HoFH

Although randomized studies cannot be performed for ethical issue, there is much clinical evidence that long-term lipoprotein apheresis can contribute to plaque regression, stabilization of angina symptoms, and improvement of prognosis[43-46]. Also, as it has been reported that an HoFH patient died of myocardial infarction due to delayed initiation of lipoprotein apheresis[46], clinicians should not hesitate in starting lipoprotein apheresis when it is necessary.

6. Supplementary Provisions

Japanese Public Financial Support

Financial assistance can be received for pediatric FH through a grant-in-aid program for chronic diseases in childhood until the age of 18 and can be extended until 20. Also, financial support for pediatric and adult HoFH patients can be applied for under Medical Aid for Chronic Pediatric Diseases of Specified Categories as well as under the category of Designated Intractable Diseases in the Japanese national health insurance scheme[47, 48].

Genetic Counseling[49]

Diagnosis of FH can impact psychosocial functioning and quality of life, so there may be a need for psychological support in routine patient care. In addition, genetic counseling is recommended for all women considering pregnancy. When one of the prospective parents has HeFH, the child has a 50% chance of having HeFH. When both prospective parents have HeFH, the child has a 25% chance of having HoFH and a 50% chance of having HeFH. However, sudden mutations are very rare. HoFH may be a serious disease but prenatal diagnosis and preimplantation diagnosis should be considered with care because the risk can be decreased by adequate treatment.

7. COI

Employment/Leadership position/ Advisory role: Akira Ohtake; Kowa Pharmaceutical Co. Ltd. Honoraria: Mariko Harada-Shiba; Kowa Pharmaceutical Co. Ltd, Amgen Astellas BioPharma K.K., Sanofi K.K. Akira Ohtake; Novo Nordisk Pharma Ltd., Eli Lilly Japan K.K., Otsuka Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., JCR Pharmaceuticals Co., Ltd., Pfizer Japan Inc., Meiji Seika Pharma Co., Ltd., Sanofi K.K.. Masatsune Ogura; Astellas Pharma Inc., Amgen Astellas BioPharma K.K., Sanofi K.K.. Shizuya Yamashita; Kowa Company, Ltd., MSD K.K./ Merck & Co, Bayer Yakuhin, Ltd, Skylight Biotech, Inc., Medical Review Co., Ltd., Amgen Astellas BioPharma K.K., Pfizer Japan Inc., Dai Nippon Printing Co., Ltd.. Atsushi Nohara; Astellas Pharma Inc., Amgen Astellas BioPharma K.K., Sanofi K.K.. Fees for promotional materials: Shizuya Yamashita; Kowa Company, Ltd., Bayer Yakuhin, Ltd, Sanwa Kagaku Kenkyusho Co.,Ltd., Otsuka Pharmaceutical Co., Ltd., Kyowa Medex Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd.. Research funding: Mariko Harada-Shiba; Astellas Pharma Inc., Kaneka Medix Corporation. Atsushi Nohara; Shionogi & Co., Ltd., Aegerion Pharmaceuticals, Inc., Alexion. Shizuya Yamashita; Takeda Pharmaceutical Company Limited., Astellas Pharma Inc., Mochida Pharmaceutical Co., Ltd.. Others: Shizuya Yamashita; Department of Community Medicine & Department of Cardiovascular Medicine Osaka University Graduate School of Medicine, Rinku General Medical Center, Kaizuka City Hospital

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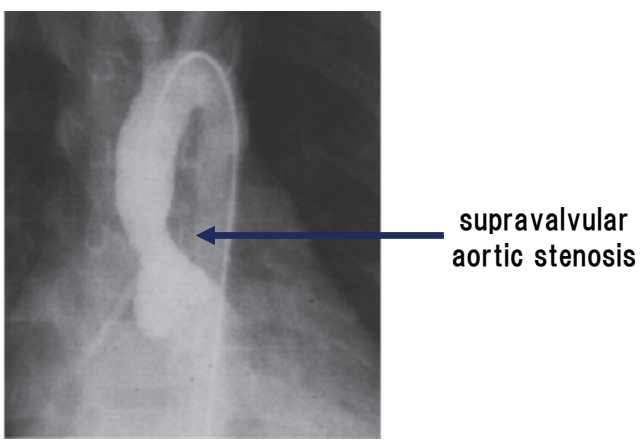
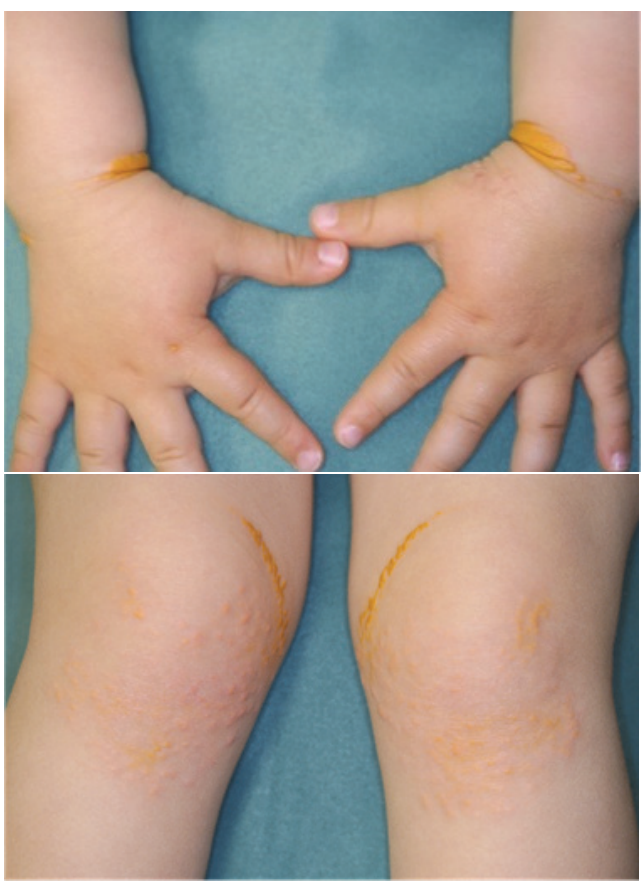


Supplementary Fig. 1. supravalvular aortic stenosis



Supplementary Fig. 2. A 3-year-old boy with skin xanthomas