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CASE REPORT

CLINICAL CASE

Intensive Combination LDL-Lowering Therapy in a Patient With Homozygous Familial Hypercholesterolemia

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ABSTRACT

We present a young boy with a diagnosis of homozygous familial hypercholesterolemia who presented with statin and ezetimibe resistance. The patient received lipoprotein apheresis at 6 years of age. His low-density lipoprotein cholesterol levels significantly were reduced by adding lomitapide and evinacumab, and his carotid plaque started to regress. (J Am Coll Cardiol Case Rep 2024;29:102367) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 1-year-old infant boy who presented with prominent plantar xanthomas in the Achilles tendons and in the skin of the wrists, legs, knees, and buttocks (**Figures 1A to 1D**) was referred to our hospital. The patient was born in 2003 and received a diagnosis of homozygous familial hypercholesterolemia (FH) in 2004 at the age of 1 year. His initial total cholesterol level was 912 mg/dL, and his low-density lipoprotein (LDL) cholesterol level was 734 mg/dL. Both of his parents exhibited Achilles tendon thickness associated with elevated LDL cholesterol levels, and they received diagnoses of heterozygous FH. On the basis of the patient's family history and the presence of an extreme phenotype, the patient received a diagnosis of homozygous familial hypercholesterolemia (HoFH).

LEARNING OBJECTIVES

- To consider intensive combination therapy including statin, ezetimibe, lipoprotein apheresis, lomitapide, and evinacumab in patients with homozygous familial hypercholesterolemia.
- To be able to achieve LDL cholesterol treatment target in patients with homozygous familial hypercholesterolemia.

PAST MEDICAL HISTORY

He had no contributory medical history and was reported not to have been given medications.

DIFFERENTIAL DIAGNOSIS

Sitosterolemia and cerebrotendinous xanthomatosis were considered.

INVESTIGATIONS

Echocardiography revealed mild aortic valve regurgitation associated with aortic valve calcification at the age of 4 years (**Figure 2**). Genetic analyses revealed compound heterozygous mutations

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ABBREVIATIONS AND ACRONYMS

ANGPTL3 = angiopoietin-like 3

FH = familial hypercholesterolemia

HoFH = homozygous familial hypercholesterolemia

LDL = low-density lipoprotein

LDLR = LDL receptor

LDLRAP1 = LDL receptor adaptor protein 1

MTTP = microsomal triglyceride transfer protein

PCSK9 = proprotein convertase subtilisin/kexin type 9

(NM_000527.5:c.418G>A [p.E140K] and NM_000527.5:c.1285G>A [p.V408M]) in the LDL receptor (*LDLR*), each of which was acquired from his parents. Some of the patient's family members had experienced sudden death, and some of his father's and mother's ancestors had received diagnoses of dyslipidemia (Figure 3). When the patient was 15 years old, his Achilles tendon thickness was 12 mm, and coronary computed tomography revealed calcification deposits at the aortic valve to the ascending aorta, with mild supravalvular aortic stenosis. However, there was no stenosis in the coronary arteries (Figure 4). Interestingly, the carotid plaque gradually regressed (maximum carotid plaque score of 12.7 to 10.4), which was associated with the further reduction of LDL cholesterol levels despite infrequent lipoprotein apheresis sessions (Figure 5).

MANAGEMENT

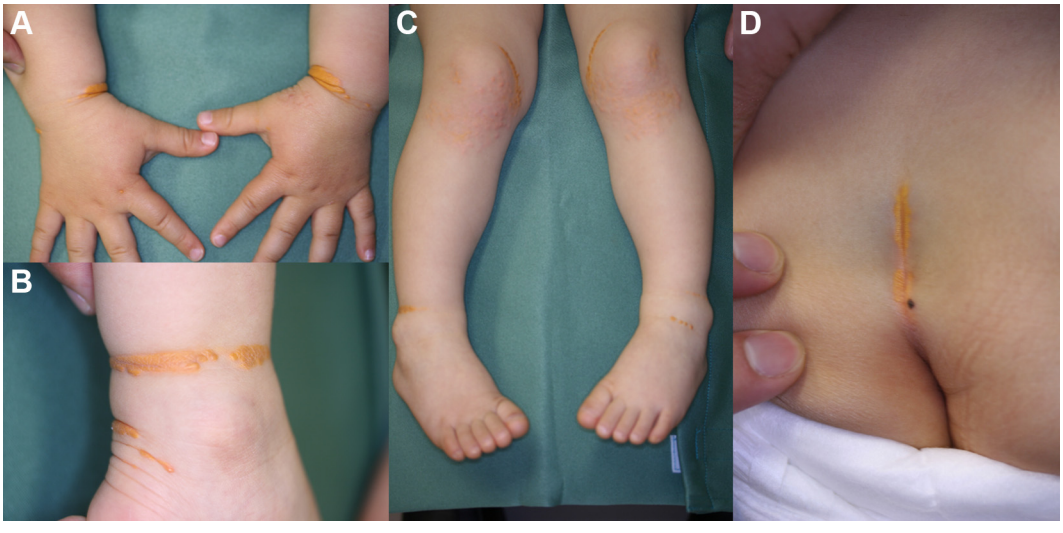
Immediately after diagnosis, treatment with atorvastatin 2.5 mg/day was initiated, which reduced LDL cholesterol levels with increased dosage. At the age of 5 years, the patient started monthly treatment with lipoprotein apheresis in addition to rosuvastatin 15 mg/day and ezetimibe 10 mg/day. His LDL cholesterol level gradually reduced with lipoprotein apheresis. However, his carotid plaque progressed (Figure 6). At the age of 14 years, therapy with evolocumab, a, proprotein convertase subtilisin/kexin type 9 (PCSK9P inhibitor, was initiated. However, it was not effective in further reducing the patient's LDL cholesterol level. Therefore, additional therapy was considered, and treatment with lomitapide (5 mg/day) was initiated. The dose was gradually escalated to a maximum dose of 40 mg/day without any overt side effects, such as stomach pain, diarrhea, or nausea. Lomitapide successfully reduced the LDL cholesterol levels, thereby inhibiting the progression of carotid plaque development. In addition to lomitapide, evinacumab was initiated at the age of 17 years and was successful in reducing LDL cholesterol levels. At the age of 18 years, the frequency of lipoprotein apheresis sessions was reduced because satisfactory LDL cholesterol levels were achieved. During long-term follow-up, the patient did not exhibit any evident side effects, including hepatic dysfunction, fatty liver, or kidney dysfunction.

DISCUSSION

Herein, we report a rare case of HoFH in which carotid plaque regression was achieved with intensive LDL cholesterol-lowering combination therapy (lomitapide and evinacumab) despite infrequent lipoprotein apheresis sessions.

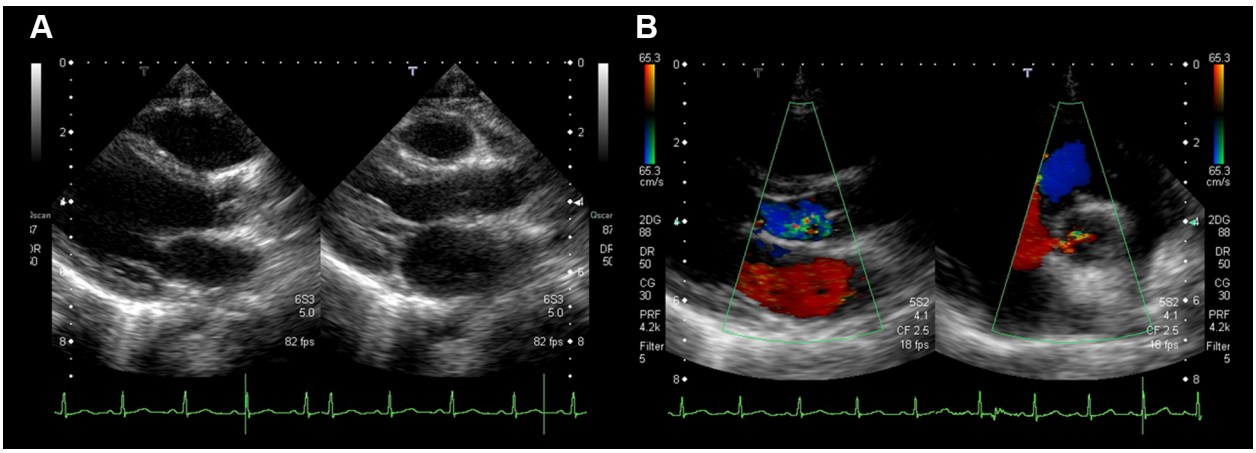
HoFH is a rare disorder, with a prevalence of approximately 1 in 360,000 people.[1-3] Individuals with HoFH exhibit xanthomas associated with

FIGURE 1 Cutaneous Xanthomas Diagnosed at 1 Year of Age



(A) Wrists. (B) Ankle (right). (C) Legs. (D) Buttocks.

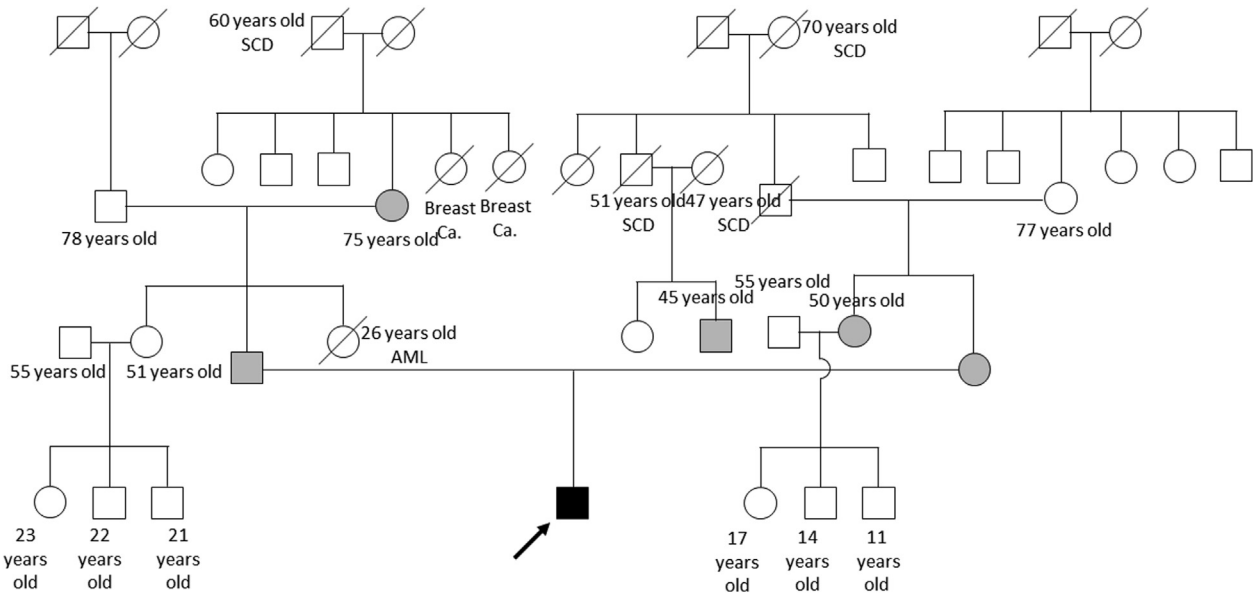
FIGURE 2 Echocardiogram at 4 Years of Age



(A) Gray-scale long-axis view (parasternal). Left (diastolic phase) and right (systolic phase) images showing calcification of ascending aorta and aortic valve. (B) Color-Doppler long and short axis views (parasternal). Left (long-axis view) and right (short-axis view) images showing aortic regurgitation.

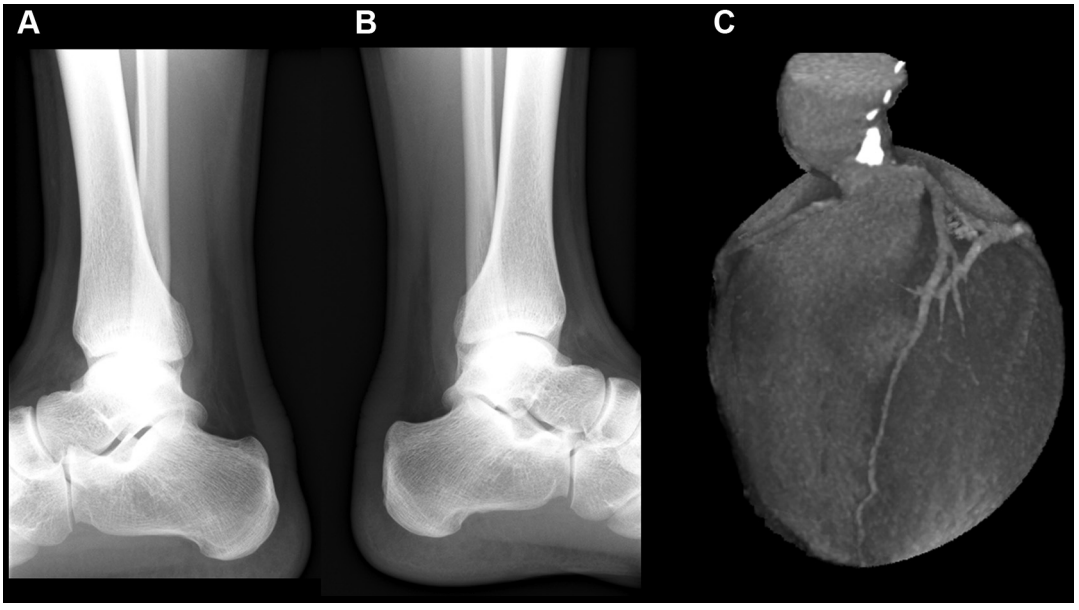
extremely elevated LDL cholesterol levels during infancy. The different types of HoFH include true homozygous FH, compound heterozygous FH, double heterozygous FH, and autosomal recessive hypercholesterolemia caused by LDL receptor adaptor protein 1 (*LDLRAP1*) mutations. The following should be noted in HoFH: First, statins are sometimes ineffective because of their lack of LDL receptor activity. Second, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor is sometimes ineffective for the same reason.[4] Third, patients should be treated as early and aggressively as possible. Fourth, patients

FIGURE 3 Family Tree



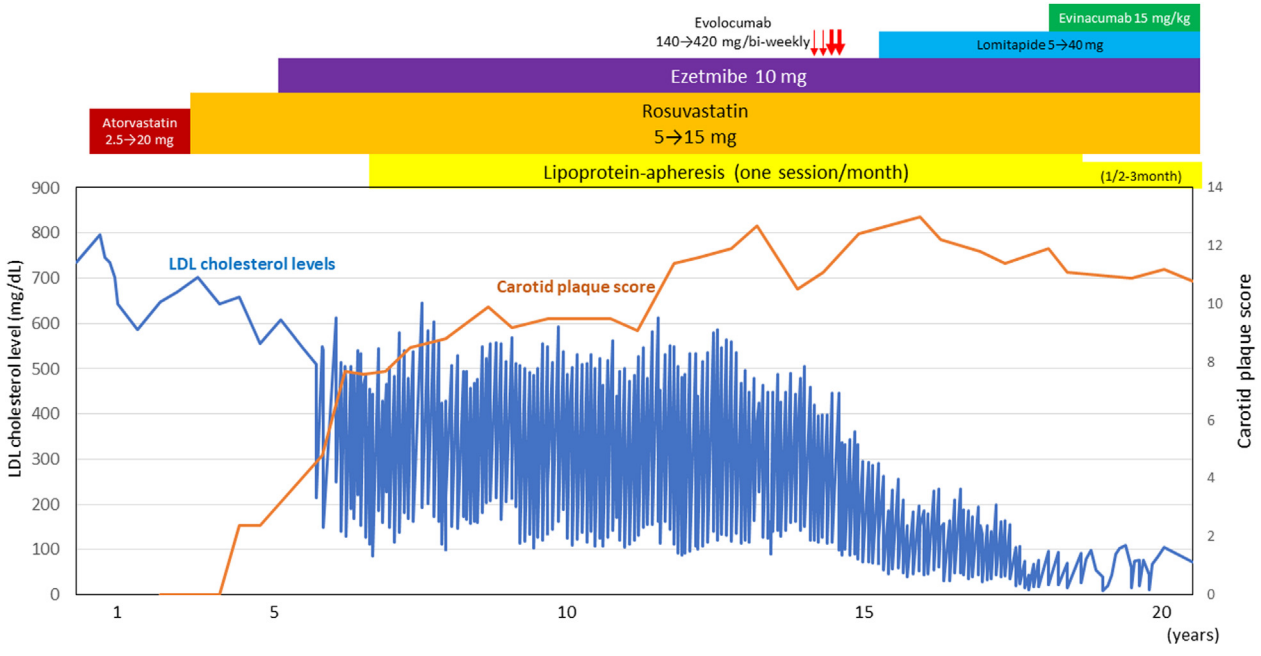
Dark square indicates the proband. AML = acute myeloid leukemia; SCD = sudden cardiac death. Gray squares indicate individuals with hyper-LDL cholesterolemia.

FIGURE 4 **Images at 15 Years of Age**



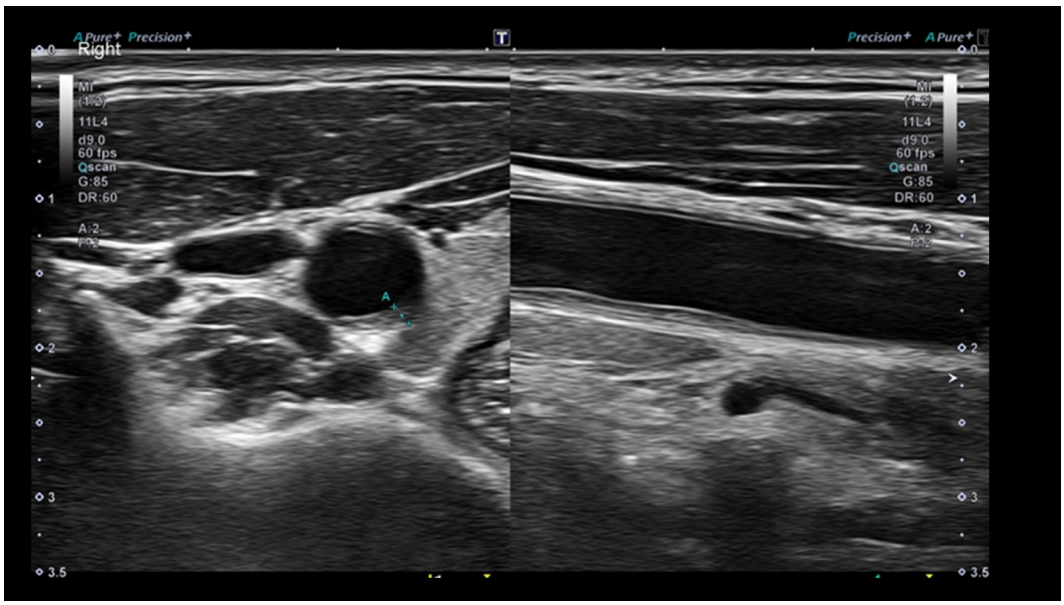
(A) Radiographic image of Achilles tendon (right). (B) Radiographic image of Achilles tendon (left). (C) Coronary computed tomography scan.

FIGURE 5 **Clinical Course**



X-axis represents age (years). Y-axis represents LDL cholesterol (mg/dL) at left and carotid plaque score at right. Blue line indicates LDL cholesterol. Orange line indicates carotid plaque score.

FIGURE 6 **Carotid Ultrasonography at 12 Years of Age**



Right (short-axis view) and left (long-axis view) images showing presence of carotid plaques.

present with premature coronary artery disease and/or supravalvular aortic stenosis if untreated or insufficiently treated. Fifth, family history information and genetic analyses are important not only for the diagnosis but also for the cascade screening of patients' relatives. Sixth, lipoprotein apheresis is required in most cases. Treatment with lipoprotein apheresis is quite effective in reducing LDL cholesterol levels and subsequent cardiovascular events in HoFH. However, it is invasive, expensive, and time consuming for patients and their caregivers. Interestingly, novel drug therapies, including microsomal triglyceride transfer protein (MTTP) and/or angiopoietin-like 3 (ANGPTL3) inhibitor, can at least reduce the frequency of lipoprotein apheresis or even discontinue it. Currently, LDL cholesterol control is inadequate, according to data from a national database.[5] Theoretically, even in HoFH, >90% reduction in LDL cholesterol levels can be achieved with the currently available combination therapies that can lower LDL cholesterol levels independently of the LDL receptor pathway.[6] To our knowledge, this is the first reported case of HoFH in which the frequency of lipoprotein apheresis could be reduced with combined lomitapide and evinacumab. MTTP and ANGPTL3 inhibitors can reduce LDL cholesterol levels via an independent pathway. Moreover, it has been suggested that the effect of ANGPTL3 inhibitor appears to be independent of the use of lipoprotein apheresis.[7] This study and others have shown that earlier and more aggressive LDL-lowering therapies in patients with FH can lead to a better prognosis.[8,9] Therefore, an ideal outcome can be achieved with combination therapy even in this most severe phenotype of HoFH. We hope that patients with HoFH can have a significantly better prognosis.

FOLLOW-UP

The patient's LDL cholesterol level and carotid plaque will be continually monitored if this positive change continues and lipoprotein apheresis can be discontinued.

CONCLUSIONS

Carotid plaque regression was successfully achieved with combined lomitapide and evinacumab despite a low frequency of lipoprotein apheresis session in a young male patient with HoFH. Furthermore, the patient had an enhanced quality of life without clinically relevant side effects. Therefore, combination therapy with lomitapide and evinacumab might be an appropriate option for patients with HoFH.

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