Journal of Clinical Lipidology (2015) 9, 234–240

Journal of Clinical Lipidology

# Clinical observations and treatment of pediatric homozygous familial hypercholesterolemia due to a low-density lipoprotein receptor defect

**Cheng-Hung Huang, MD, MS, Pao-Chin Chiu, MD, Hao-Chuan Liu, MD, Yung-Hsiu Lu, MS, Jun-Kai Huang, MS, Min-Ji Charng, MD, PhD**[**1], Dau-Ming Niu, MD, PhD**[*1]**

*Institute of Clinical Medicine, National Yang–Ming University, School of Medicine, Taipei, Taiwan, R.O.C (Drs C-H. Huang, Lu, and Niu); Department of Pediatrics, Taipei Veterans General Hospital, Taipei, Taiwan, R.O.C (Drs C-H. Huang, Liu, Lu, J-K. Huang, and Niu); Department of Pediatrics, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, R.O.C (Dr Chiu); School of Medicine, National Yang–Ming University, Taipei, Taiwan, R.O.C (Dr Charng); and Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, R.O.C (Dr Charng)*

**KEYWORDS:**
Homozygous familial hypercholesterolemia;
LDL receptor;
Total cholesterol;
Statin;
Ezetimibe;
LDL apheresis;
Liver transplantation

**BACKGROUND:** Clinical observation and treatment of children with homozygous familial hypercholesterolemia (HoFH) has rarely been reported. We report clinical observations and treatment of 10 ethnic Chinese children with HoFH due to low-density lipoprotein receptor (LDLR) defect.

**OBJECTIVES:** In children with HoFH, we evaluated the response to conventional cholesterol-lowering drug therapy and performed LDLR gene analysis.

**METHODS:** A retrospective review of lipid profile changes in pediatric patients diagnosed with HoFH seen in our pediatric endocrinology outpatient clinic was performed. HoFH was diagnosed by molecular study of these patients and their parents.

**RESULTS:** One novel (c.64del G) and 12 known mutations were found in the LDLR gene. Mutation of p.C308Y was the most common and was found in 26% of the studied alleles.Seven patients had fair responses to conventional drug therapy (high-dose statin with ezetimibe) with a reduction of 50% or more of the total cholesterol levels. The low-density lipoprotein–cholesterol levels of three patients decreased to lower than 160 mg/dL. One who had a good response to conventional drug therapy developed significant atheromatous plaques (largest plaque: 7.4 × 2.7 cm) in the extracranial carotid arteries and myocardial ischemia changes at 11 years old.

**CONCLUSION:** The results suggest that despite aggressive therapy, many patients are not well controlled; atherosclerosis may progress, and novel therapies are required.


Familial hypercholesterolemia (MIM#143890) is an inherited, autosomal, codominant disorder that may be caused by defects in the gene encoding the low-density lipoprotein (LDL) receptor (LDLR)[1–4] but also can be caused by mutations in other genes. The heterozygous form of familial hypercholesterolemia (HeFH), in which

[1] Contributed equally.

* Corresponding author. Department of Pediatrics, Taipei Veterans General Hospital, 201 Shih-Pai Road, Section 2, Taipei 112, Taiwan, R.O.C.
** Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, 201 Shih-Pai Road, Section 2, Taipei 112, Taiwan, R.O.C.
E-mail address: mjcharng@vghtpe.gov.tw; dmniu1111@yahoo.com.tw
Submitted May 6, 2014. Accepted for publication November 25, 2014.

1933-2874/
http://dx.doi.org/10.1016/j.jacl.2014.11.011

only a single mutant LDLR allele is present, occurs at a frequency of 1:200 to 1:500 in the general population.[5] HeFH is characterized by high cholesterol levels, specifically LDL in the blood, and early cardiovascular disease (CVD, usually approximately 30–40 years old). Treatment for high cholesterol levels in HeFH patients is usually more difficult than in patients without HeFH. Higher doses of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statin) usually are necessary for effective cholesterol control in HeFH patients. Patients who are homozygous (homozygous familial hypercholesterolemia [HoFH]) for the LDLR gene defect are very rare and are found at a frequency of 1 in 1,000,000.[6,7] However, recent studies have suggested that the prevalence of both HeFH and HoFH might be greater than previously thought.[5,8] HoFH patients have severe hypercholesterolemia and develop severe CVD as early as childhood.[9–12] Drugs are largely not effective enough for HoFH patients. Only more aggressive therapies, such as LDL apheresis or liver transplantation combined with cholesterol-lowering drugs can maintain cholesterol at an acceptable level.[13]

In this study, we reviewed 10 Chinese children with HoFH due to LDLR defects and found that 6 of them were able to maintain their total cholesterol level around or below 240 mg/dL (the upper limit of the normal range of total cholesterol levels at our laboratory) after a high dosage of HMG-CoA reductase inhibitors and ezetimibe therapy. Because of young age of these patients, we did not use maximum dose of statin. LDL cholesterol (LDL-C) levels in 3 of the 6 patients had decreased to less than 160 mg/dL (the upper limit of the normal range of LDL-C levels in our laboratory) after a high dosage of HMG-CoA reductase inhibitor combined with ezetimibe. Herein, we report the detailed clinical, biochemical, and molecular genetic characteristics and the treatment course of these 10 ethnic Chinese pediatric patients.

## Patient characteristics and clinical observations

First, we divided the 10 patients into two groups. Patients who showed 50% or more reduction of their total cholesterol levels after conventional cholesterol-lowering drug therapy were classified as “responders,” and the other patients were classified as “poor responders.”

## Responders

Seven patients (cases 1–6, 8) were placed in the responder group (Table 1). The initial manifestation of these patients was multiple cutaneous xanthomata that occurred in early childhood. The total cholesterol levels of these cases before treatment were approximately 384 to 848 mg/dL. We started treatment with ezetimibe only or combined with HMG-CoA reductase inhibitor at our institution. For those without a significant response to ezetimibe only, HMG-CoA reductase inhibitors were added. The total cholesterol level of the patients in this group is decreased by approximately 50% to 68%.

Case 8 had an initial total cholesterol level of 848 mg/dL. Although the decrease in the total cholesterol level after high-dosage statin and ezetimibe therapy was 57.8%, the total cholesterol level was still persistently higher than 350 mg/dL. Because the parents were reluctant to have LDL apheresis for their child, this therapy was postponed. The carotid Doppler scan was performed regularly each year since her age of 6. At the age of 11 years, significant atheromatous plaques (largest plaque: 7.4 × 2.7 cm) in the extracranial carotid arteries were noted. The thallium myocardial perfusion scan (TL-201 scan) also showed myocardial ischemia changes at the anterior wall of the heart. She finally started to receive LDL apheresis, but, unfortunately, it was discontinued several months later because of arteriovenous shunt stenosis. Now, she is on the list for lomitapide clinical trial for children with HoFH in 2014. Discussions with both the US Food and Drug Administration and European Medicines Agency to finalize the trial protocol design are ongoing.[14]

## Poor responders

Case 7 has the same genotype as case 1. However, the patient’s response to high-dosage statin therapy was not as good as that of case 1. Her initial total cholesterol level was 672 mg/dL, which was higher than the initial cholesterol level (595 mg/dL) of case 1. After a high-dosage statin and ezetimibe therapy, the total cholesterol level decreased to 37.1%, which was lower than that of case 1 at 57.8%. This finding indicates that their modified factors may influence the manifestations of the homozygous LDLR defect.

The pretreatment total cholesterol level of case 9 was extremely high (1242 mg/dL). Two mutations (c.64del G; c.1953-1954 delTA) of the LDLR gene were identified in this patient. One mutation, c.1953-1954 delTA, was inherited from his mother, and the novel mutation (c.64del G) appeared de novo, not from the consanguineous father. After high-dosage statin and ezetimibe therapy, the total cholesterol level did not change significantly. Thereafter, his xanthomas increased and enlarged rapidly. Because of the reluctance of the parents to consider LDL apheresis, he received a living-donor liver transplantation from his father at 3 years of age. His total cholesterol level decreased to normal promptly after transplantation, and his cholesterol levels remained within normal ranges during follow-up.

The pretreatment total cholesterol level of case 10 was greater than 800 mg/dL. After high-dosage statin and ezetimibe therapy, the total cholesterol level decreased to approximately 650 mg (21.5% reduction). After 14 years of age, he started to receive LDL apheresis in addition to statin therapy (40 mg/d simvastatin). His total cholesterol level was controlled at 200 to 300 mg/dL between each