Phenotypic homozygous familial hypercholesterolemia successfully treated with proprotein convertase subtilisin/kexin type 9 inhibitors

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Title

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DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are available as part of the article, and no additional data sources are required.

FUNDING STATEMENT

None.

CONFLICT OF INTEREST DISCLOSURE

None to declare.

ETHICS APPROVAL STATEMENT

This study was conducted in accordance with the declaration of Helsinki.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from the patient for publication in accordance with the journal's patient consent policy.

Key Clinical Message

Recent data reveal phenotypic HoFH patients may be responsive to PCSK9 inhibitors, challenging prior assumptions. Genetic testing advancements now more accurately forecast patient responses to these therapies, improving treatment strategies.

Keywords

homozygous familial hypercholesterolemia, pediatric familial hypercholesterolemia, proprotein convertase subtilisin/kexin type 9 inhibitors, genetic testing

Main text

INTRODUCTION

Familial hypercholesterolemia (FH) is a genetic lipoprotein disorder characterised by elevated plasma low-density lipoprotein cholesterol (LDL-C) levels and early onset of atherosclerotic premature coronary artery disease (PCAD).[1-3] This condition manifests distinct clinical features such as xanthomas, thickening of the Achilles tendon, and corneal rings, which often serve as clinical pointers even before genetic confirmation. In particular, homozygous familial hypercholesterolemia (HoFH) is a severe form, presenting with xanthomas and supravalvular aortic stenosis from early childhood and requiring different management from heterozygous familial hypercholesterolemia (HeFH).[4,5]

In this case, cutaneous xanthomas before the age of 10 years, thickening of the Achilles tendon, and high levels of LDL-C were suspected to be homozygous HoFH. Historically, our understanding of FH, especially HoFH, suggested that this form was generally unresponsive to proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, primarily because of the absence of low-density lipoprotein (LDL) receptor activity.[6] This viewpoint has significantly influenced pharmacotherapeutic decisions, often limiting the available treatment options for patients. This paper reports a case of phenotypic HoFH that was successfully treated with PCSK9 inhibitors.

CASE REPORT

Case history/Examination

A 29-year-old woman presented with cutaneous xanthomas before the age of 10 years and had undergone multiple resections of xanthomas in her teens. The patient was referred to our hospital when xanthomas reappeared. She had Achilles tendon thickening, nodular xanthoma on the elbows, and palpebral xanthoma. No palmar xanthomas or corneal rings were observed.

She had a smoking history of 10 cigarettes per day since the age of 20 years with minimal alcohol consumption. In terms of her family history, her mother suddenly died at the age of 60 years. While the exact cause remains unknown, the circumstances could not rule out the possibility of PCAD. Additionally, her sister had undergone multiple resections for xanthomas during childhood.

On examination, her temperature was 36.0; her blood pressure was 108/68 mm Hg; her pulse was 60/min; and her oxygen saturation was 98% on ambient air. Blood tests revealed total cholesterol (TC) of 429 mg/dL, low-density lipoprotein cholesterol level of 357 mg/dL, high-density lipoprotein cholesterol (HDL-C) of 45 mg/dL, triglyceride (TG) of 136 mg/dL, and lipoprotein (a) of 20.2 mg/dL. The Achilles tendon showed a thickening of 15 mm on radiography.

Differential diagnosis and investigations

In this patient, cutaneous xanthomas before the age of 10 years, thickening of the Achilles tendon, and a high LDL-C were suggestive of phenotypic HoFH. We also considered other genetic lipid disorders, such

as sitosterolemia, lysosomal acid lipase deficiency, and cerebrotendinous xanthomatosis. However, the patient exhibited normal sitosterol and lysosomal acid lipase activities. In addition, the patient showed no neurological symptoms typically associated with cerebrotendinous xanthomatosis.

Following a comprehensive discussion with the patient about the risks, benefits, and implications of genetic testing, informed consent was obtained, and genetic testing was performed. Genetic testing by next-generation sequencing (NGS) through exome analysis targets 22 genes associated with lipid metabolism abnormalities including low-density lipoprotein receptor (*LDLR*), apolipoprotein B (*APOB*), proprotein convertase subtilisin/kexin type 9 (*PCSK9*), low-density lipoprotein receptor adaptor protein1(LDLRAP1), ATP binding cassette subfamily G member 5 (*ABCG5*), ATP binding cassette subfamily G member 8 (*ABCG8*), apolipoprotein E (*APOE*), and cytochrome P450 family 27 subfamily A member 1 (*CYP27A1*) detected no pathogenic or likely pathogenic variant. In addition, multiple ligation-dependent probe amplifications (MLPA) of *LDLR* revealed a large deletion in exons 7-14.

Outcome, treatment, and follow-up

Based on these results, the patient was diagnosed with phenotypic HoFH. Initial therapy with maximum tolerated doses of rosuvastatin and ezetimibe reduced the LDL-C levels to 152 mg/dL. However, a target LDL-C level of <55 mg/dL was not achieved. Treatment with a PCSK9 inhibitor (evolocumab) was initiated, considering the residual LDL receptor activity. This intervention proved highly effective, decreasing the patient's LDL-C level to 22 mg/dL (Table 1). No medication side effects were observed, adequate LDL-C control was achieved, and the palpebral xanthoma regressed. Written informed consent was obtained from the patient for publication in accordance with the journal's patient consent policy.

DISCUSSION

There are two primary classifications of FH: HeFH and HoFH. Individuals with HeFH possess one pathogenic variant and show an abnormal biochemical phenotype. In contrast, those with genotypic HoFH have two variants, which lead to more severe LDL-C deviations and symptoms. The primary genes associated with these conditions include *LDLR* ,*APOB* , *PCSK9* , and *LDLRAP1* .[7] To ensure clarity and avoid misinterpretation, the recent guidelines recommend using the term "phenotypic HoFH" as a concise clinical descriptor when a genetic diagnosis is not confirmed.[8]

This case involved a patient who was initially considered to have phenotypic HoFH. The patient responded well to PCSK9 inhibitors, and detailed genetic testing confirmed the diagnosis of HeFH. This case study highlights two important aspects. Some cases of phenotypic HoFH are notably treated with LDL receptor-mediated pharmacotherapy, including PCSK9 inhibitors. Second, in cases of phenotypic HoFH, detailed genetic testing may help predict the responses to these pharmacotherapies (Figure 1).

HoFH is known to be ineffective with LDL receptor-mediated pharmacotherapy, and LDL apheresis might be considered a treatment option.[9] HoFH typically exhibits a near-complete absence of LDL receptor activity, making it less responsive to pharmacotherapy, such as statins and PCSK9 inhibitors, by upregulating LDL receptors. Conversely, patients with HeFH retain some LDL receptor activity and may benefit significantly from these pharmacotherapies. The term "phenotypic HoFH" generally encompasses not only true homozygotes but also double heterozygotes and compound heterozygotes.[10] However, the patient exhibited phenotypic HoFH, but genetic testing indicated that she was heterozygote with large-scale copy number variations (CNVs) deletion. In this case, it was revealed that this type also exhibited phenotypic HoFH. Furthermore, HoFH in true homozygotes typically exhibits a near-complete absence of LDL receptor activity; however, there is potential for residual LDL receptor activity in heterozygotes. Therefore, these individuals may benefit from LDL receptor-mediated pharmacotherapy. In this case, the patient exhibited phenotypic HoFH but was suspected to retain some LDL receptor activity. This residual activity likely contributes to the notable effectiveness of the PCSK9 inhibitor.

Further, in cases of phenotypic HoFH, detailed genetic testing may help predict the responses to these pharmacotherapies. The detection rate of pathogenic variants in clinically diagnosed cases of FH is reportedly

approximately 60–80%.[11,12] Genetic testing for FH is not mandatory; it can make the diagnosis of FH more definitive, and if the originator has been genetically tested, the diagnosis of FH in the family is also assured.[13,14] There are several methods of genetic testing. NGS is renowned for its ability to sequence millions to billions of DNA strands simultaneously.[15] This allows for a broad examination of substantial genomic regions in a single run. However, implementing this approach is challenging. While NGS can potentially detect variations, such as single nucleotide variants, insertions, and deletions, it is sometimes less reliable for detecting CNVs.

In contrast, MLPA is used to detect large-scale deletions or amplifications of genes that are difficult to analyse using whole-gene sequencing methods. The data derived from MLPA are quantitative, rendering an accurate representation of CNVs compared to NGS.[16] However, they are limited in scope and are incapable of detecting single-nucleotide variants (SNVs). Most of the pathogenic variants of FH cases are SNVs in *LDLR* , but approximately 10% are attributed to CNVs in*LDLR* .[17] Therefore, a single genetic test on one side alone may not detect the genetic mutation or may be misjudged. Detailed genetic testing combining multiple genetic tests may provide an efficient algorithm for the genetic testing of FH[18]. It may be useful in assessing residual LDL receptor activity and predicting the response to these pharmacotherapies in cases exhibiting phenotypic HoFH. The point of our case lies in the phenotypic HoFH patient who demonstrated an unexpectedly positive response to PCSK9 inhibitors, emphasising the need for a deeper dive into individual genetic phenotypes.

Limitation

Some cases of phenotypic HoFH are notably responsive to LDL receptor-mediated pharmacotherapy, including PCSK9 inhibitors, and detailed genetic testing may help predict the response to these pharmacotherapies. However, further studies are needed to confirm these hypotheses. For cases where PCSK9 inhibitors are ineffective, recent developments in angiopoietin-like protein 3 (ANGPTL3) inhibitors, which have shown efficacy even in HoFH cases without LDL receptor activity, offer a promising avenue.[19] ANGPTL3 inhibitors offer the potential to attain the LDL-C goal or reduce the need for LDL apheresis and show promising potential for determining optimal pharmacotherapies in the future.

Conclusion

While HoFH is traditionally considered ineffective with LDL receptor-mediated pharmacotherapy, there are phenotypic HoFH cases that demonstrate notable effectiveness with treatments such as PCSK9 inhibitors. Detailed genetic testing may help predict responses to these pharmacotherapies.

Figure 1

HoFH, homozygous familial hypercholesterolemia; LDL, low-density lipoprotein; CNVs, copy number variations; PCSK9, proprotein convertase subtilisin/kexin type 9; ANGPTL3, angiopoietin-like protein 3.

Table 1

Lipid profile of the patient.

Author Contributions

Ryosuke Tani: Conceptualisation, data curation, investigation, resources, and writing the original draft.

Keiji Matsunaga: Supervision; writing review and editing.

Yuta Toda: Data curation; investigation.

Tomoko Inoue: Data curation; investigation.

Hai Ying Fu: Data curation; investigation.

Tetsuo Minamino: Supervision; writing review and editing.

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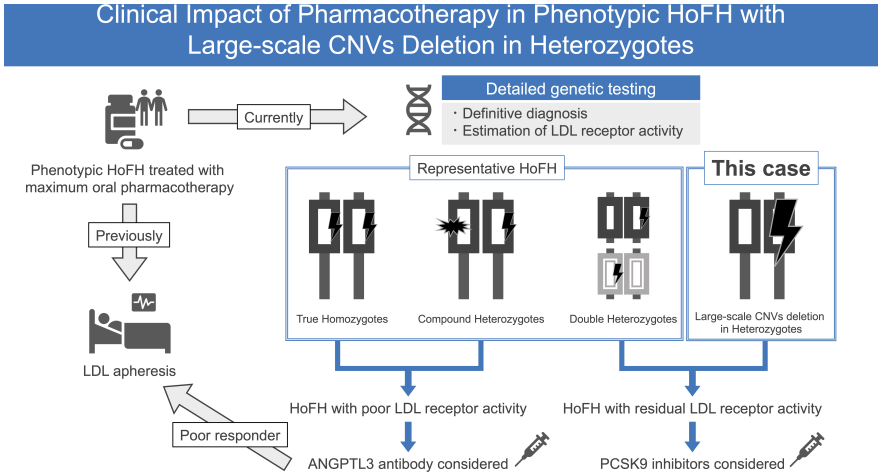

Time	TC (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)	Pharmacotherapy
Day 0	429	357	45	136	
					Pitavastatin 2mg
					Ezetimibe 10mg
Day 28	303	246	44	65	
					Rosuvastatin 10mg
					Ezetimibe 10mg
Day 70	220	152	48	99	
					Rosuvastatin 20mg
					Ezetimibe 10mg
					Evolocumab 420mg q4w
Day 230	91	22	48	103	

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride.