

# Familial Hypercholesterolemia and Cerebral Infarction - A Case Report

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## Case report

**Keywords:** Familial hypercholesterolemia, Cerebral infarction, Xanthoma, LDLR gene

**Posted Date:** April 5th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-377280/v1>

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# Abstract

**Background:** Familial hypercholesterolemia has various presentations mostly including early-onset cardiovascular diseases, remarkable skin and tendon xanthomas. By comparison, Cerebral Infarction due to familial hypercholesterolemia is extremely rare.

**Case presentation:** We present a 41-year-old man who was admitted to our hospital with dizziness, vertigo, slurred speech, weakness in his left limbs. He had family history of Hyperlipidemia in older sister. Head CT scan demonstrated multiple acute cerebral infarction in the right frontal and parietal lobes, and arterial plaques was found in the bifurcation of common carotid artery. The severe carotid stenosis was located in the initial segment of the right internal carotid artery. Histopathologic findings were consistent with xanthoma. Especially, molecular analysis of the LDLR gene was made, which identified heterozygous missense mutation in exon 12 of the LDLR gene. The final diagnosis of cerebral infarction associated with familial hypercholesterolemia was made. The patient was referred to a nutritionist for dietary advice, and was treated with Tab. Finally, the patient recovered well. The symptoms of brain infarct vanished and no recurrence occurred during follow-up.

**Conclusions:** In the present case, the acute cerebral infarction is most likely due to hypercholesterolemia, as his family history of hypercholesterolemia, and arterial plaques and severe carotid stenosis was found by CTA. This case highlights the importance of the early diagnosis and treatment of hypercholesterolemia, which may help in preventing the development of cardiovascular and cerebrovascular diseases.

## Background

Familial hypercholesterolemia is a genetic disorder, which due to mutation in low-density lipoprotein (LDL) receptor gene. The mutation prevents hepatic cells from removing serum LDL-cholesterol and results in hypercholesterolemia [1]. The general characterization of heterozygous FH is by elevated low-density lipoprotein (LDL) cholesterol and early-onset cardiovascular diseases, remarkable skin and tendon xanthomas [2]. Herein, we present a patient with familial hypercholesterolemia who presented with Cerebral Infarction. Especially, molecular analysis of the LDLR gene was made, which identified heterozygous missense mutation in exon 12 of the LDLR gene. Owing to its scarcity, with the consent of the patient, we herein present this case for discussing the reason for its rarity and sharing our experience of management.

## Case Presentation

A 41-year-old man was admitted to the hospital due to acute onset of Cerebral Infarction in May 2017. He experienced acute-onset symptoms, accompanied also by dizziness, vertigo, slurred speech, weakness in his left limbs for 4h prior to admission. He had family history of Hyperlipidemia in older sister. On physical examination, he and his older sister both had arcus corneae (Fig. 1A,B,C,D), and less obvious

signs of cutaneous xanthomas manifesting as firm, smooth, nodular thickening of the hands and knees(Fig. 2A,B).

Laboratory investigation showed total serum cholesterol level of 11.45 mmol/l and the low-density lipoprotein (LDL) 8.24 mmol/l. Levels of high-density lipoprotein (1.24mmol/l), triglyceride(0.64mmol/l) and Glycated hemoglobin (5.4%)were normal. Table 1 shows the lipid profile of the patient. Other family members were also investigated for lipid profile (Table 2).

Subsequent head and neck CT angiography (CTA) was performed, Head CT scan demonstrated multiple acute cerebral infarction in the right frontal and parietal lobes, and arterial plaques was found in the bifurcation of common carotid artery. The severe carotid stenosis was located in the initial segment of the right internal carotid artery. Chest CT scan demonstrated aortic and coronary artery calcification.

A biopsy specimen (Fine-needle biopsy) removed from the nodule of the left hand. On microscopy it shows multiple cholesterol crystals surrounded by granuloma formation, and infiltrated with admixture of multinuclear giant cells, foamy histiocytes and vasoactive compounds(Fig. 3A,B,C,D).

With the consent of the patient, molecular analysis of the LDLR gene was made. Blood samples were acquired from the patient. Genomic DNA was isolated from whole blood using QIAamp DNA Mini Kit (QIAGEN) according to standard manufacturer's protocol. Qualitative and quantitative estimations were carried out on the DNA samples. Targeted next-generation sequencing (TNGS) was implemented for comprehensive genetic analysis for the known and novel mutations in hot spots within exons and exon–intron boundaries of LDLR, APOB, LDLRAP1, PCSK9, ABCG5, ABCG8, LIPA, LPL, APOA5, LIPI, USF1, APOE, LIPC, ABCA1, LCAT, APOA1, HAMP, HFE, HFE2, SLC40A1, and TFR2. We identified one suspected pathogenic variant [c.1747 > T, p.(His583Tyr)], which was heterozygous and missense mutation in exon 12 of the LDLR gene (Table 3).

Based on the clinical, laboratory, imaging features, histologic, and molecular analysis of the LDLR gene, a diagnosis of cerebral infarction associated with familial heterozygous hypercholesterolemia was made.

The patient was referred to a nutritionist for dietary advice, and was treated with Tab. Atorvastatin 40 mg for blood lipid reduction, aspirin enteric-coated tablet 100 mg and bisulfate clopidogrel 75 mg both for resist blood platelet aggregation and thrombopoiesis. The patient recovered well. His lipid profile 6 months later is given in Table 1. The cutaneous xanthomas have flattened. The symptoms of brain infarct vanished and no recurrence occurred during follow-up.

## Discussion

Familial hypercholesterolemia (FH) resulting from mutations in the low-density lipoprotein (LDL)–receptor gene is associated with increased risk of premature atherosclerosis and coronary artery disease[3]. Occasionally, patients may be totally asymptomatic. Generally, this pathology is found

incidentally during a routine physical examination or in the process of unrelated clinical problems[4]. In our case, hypercholesterolemia was found due to the occurrence of cerebrovascular disease.

Physical signs present in many, but not all, patients and result from cholesterol deposits affecting the corneal margins (arcus corneae), skin of eyelids (xanthoema) and extensor tendons especially the Achilles and extensor tendons of the hands (xanthomas) [5]. In our case, we only found arcus corneae, and less obvious signs of cutaneous xanthomas.

Because xanthomas are benign lesions, a number of cases do not need surgical treatment. Frequently, fine-needle biopsy is the main choice for histologic identification[6]. In our case, we get the biopsy specimen by fine-needle. Microscopically, it shows multiple cholesterol crystals surrounded by granuloma formation, and infiltrated with admixture of multinuclear giant cells, foamy histiocytes and vasoactive compounds suggestive of xanthoma.

Under normal physiological conditions, the LDL receptors regulate the uptake of cholesterol but a defect in the mechanism for clearing LDL could lead to FH. The defect can result from mutations in the Low density lipoprotein receptor gene (LDLR), Apolipoprotein B-100 gene (APOB), and Proprotein convertase subtilisin/kexin type 9 gene (PCSK9) genes[7]. The LDLR gene is located on chromosome 19p13.1–13.3 which spans 45 kb and comprises of 18 exons and 17 introns encoding a mature protein of 839 amino acids[8]. Mutations of the LDLR gene such as nucleotide substitutions, deletions and insertions, as well as rearrangements can cause FH. The previous report in Asia have identified a novel mutation at position c.2132 in exon 14 translating the wildtype amino acid cysteine (711C) to a nonsynonymous missense tyrosine (711Y) [9]. In our case, we identified the mutation at position c.1747C > T in exon 12 for His583Tyr.

## Abbreviations

FH: Familial hypercholesterolemia; LDL: low-density lipoprotein; CTA: CT angiography; Tab: tablet.

## Declarations

### Acknowledgements

Not applicable.

### Authors' contributions

Yang Jingjing and Liang Zhanhua conceived the case report.

Jiang Huajun drafted the manuscript.

Qu Wei revised the manuscript.

Both authors read and approved the final manuscript.

## **Funding**

Not applicable.

## **Availability of data and materials**

Not applicable.

## **Ethics approval and consent to participate**

Not applicable.

## **Consent for publication**

Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

## **Competing interests**

The authors declare that they have no competing interests.

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# Tables

**Table 1:** Lipid profile of the patient

	On admission	6 months later
Total chol	11.45	6.79
HDL	1.24	1.20
LDL	8.24	4.38
Triglycerides	0.64	1.36

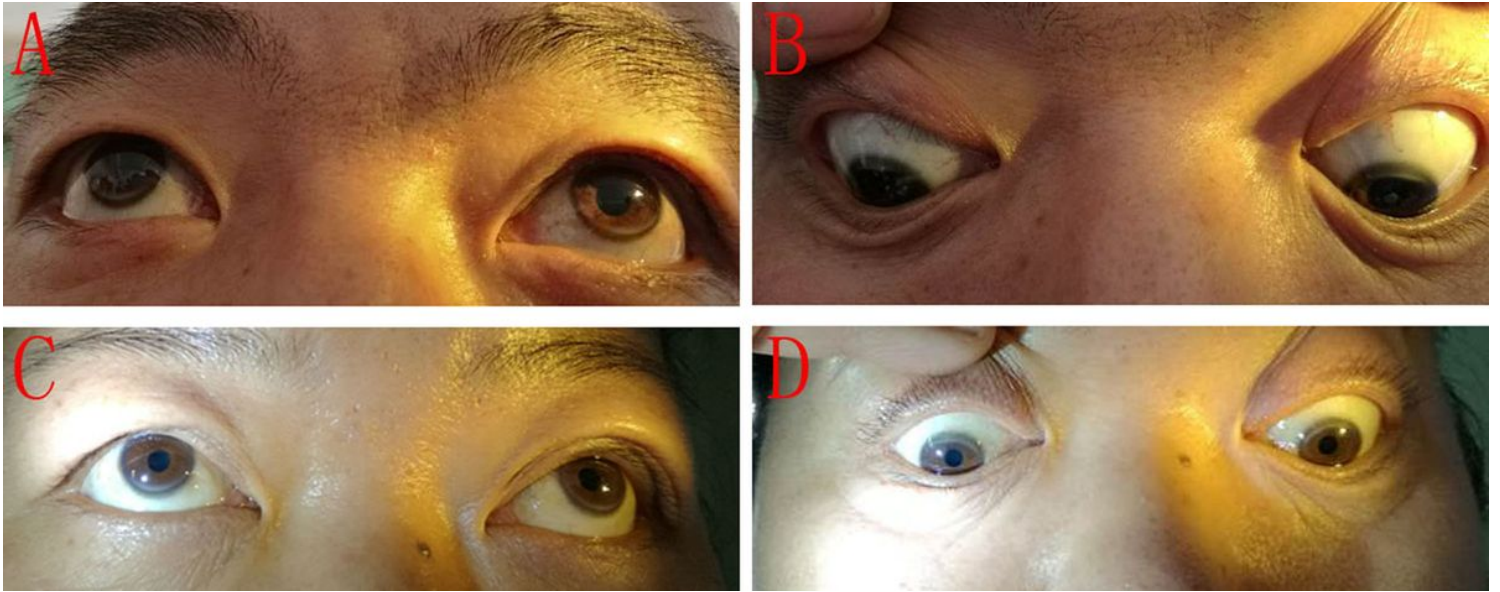
**Table 2:** Lipid profile of the patient’s family

	Patient	Sister(42 years)	son(19 years)
Total chol	11.45	10.03	5.44
HDL	1.24	1.28	1.03
LDL	8.24	7.22	3.44
Triglycerides	0.64	0.93	0.97

**Table 3:** one suspected pathogenic variant

Gene	Exome	Coding region changes	Amino acid changes	Zygosity	pathogenic
LDLR					
(NM_000527.4)	12	c.1747>T	p.(His583Tyr)	Heterozygous	Possibly damaging

# Figures



**Figure 1**

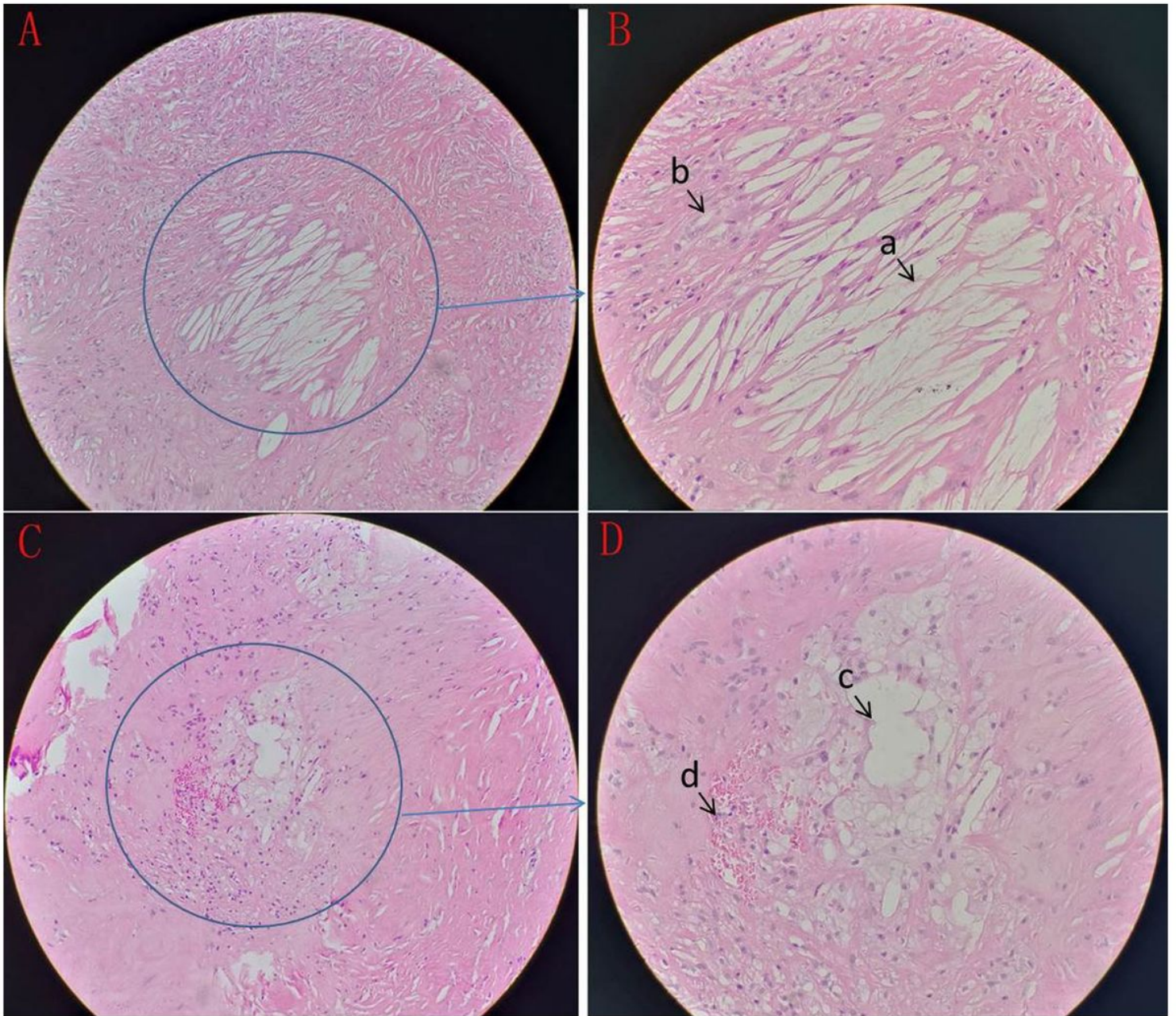
arcus corneae. A and B: the Hospitalized patient; C and D: his older sister.



**Figure 2**

less obvious signs of cutaneous xanthomas. A:left hand(black arrow); B: right knee(black arrow).





**Figure 3**

Multiple cholesterol crystals(a) surrounded by granuloma formation, and infiltrated with admixture of multinuclear giant cells(b), foamy histiocytes(c) and vasoactive compounds(d). A and B at the same field of vision, while C and D at the same field of vision(A and C: hematoxylin and eosin 100; B and D: hematoxylin and eosin 400).