

# The use of high-resolution MRI to detect thrombosis and lipid-rich carotid artery plaques in a patient with homozygous familial hypercholesterolemia

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## SUMMARY

*Homozygous familial hypercholesterolemia is a rarely genetic disorder of the lipoprotein metabolism intimately related to premature atherosclerotic cardiovascular disease that can lead to high disability and mortality. Homozygous familial hypercholesterolemia typically affects not only the aortic root, compromising the coronary ostia, but also affects other territories such as the carotid, descending aorta, and renal arteries. Multi-contrast high-resolution magnetic resonance imaging (MRI) provides a validated and useful method to characterize carotid artery atherosclerotic plaques quantitatively. However, very few studies have been done on assessing plaque composition in patients with Homozygous familial hypercholesterolemia using high-resolution MRI. This report is to evaluate the value of MRI in accessing carotid artery disease in patients with Homozygous familial hypercholesterolemia. We describe a 28-year-old patient from Beijing, China, who presented to the Neurology Clinic with intermittent blurred vision of the right eye, headache, nausea, and vomiting for eight years without obvious causes. Familial hypercholesterolemia was suspected based on medical history and laboratory examination. Carotid Doppler ultrasound showed bilateral common carotid artery, internal carotid artery, and external carotid artery wall thickening with hyperechoic signals. Subsequently, high-resolution multi-contrast MRI of the carotid showed calcification with hypo-intense areas located at the middle layer of the plaque, with moderate stenosis. The plaque located at the right bifurcation of the common carotid artery extended to the internal carotid artery, causing lumen stenosis close to occlusion. The patient was treated with right carotid artery endarterectomy. At a 6-month follow-up, there had been no recurrence of the patient's symptoms.*

**KEYWORDS:** Magnetic Resonance Spectroscopy. Plaque, Atherosclerotic. Carotid Intima-Media Thickness. Carotid Arteries. Hyperlipoproteinemia Type II.

## INTRODUCTION

Homozygous familial hypercholesterolemia (HoFH) characterized clinically by plasma cholesterol levels >13 mmol/L, extensive xanthomas, and followed by markedly premature and progressive atherosclerotic

cardiovascular disease (ACVD) is a rare and life-threatening disease<sup>1</sup>. ACVD typically affects the aortic root, compromising the coronary ostia, but also other territories such as the carotid, descending aorta, and

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renal arteries<sup>2</sup>. Cholesterol and calcium deposits, as well as artery wall fibrosis and inflammation, can lead to lumen stenosis<sup>3</sup>. In the last two years, several guidelines have been published in an attempt to improve FH diagnosis and treatment<sup>4,5</sup>. Multi-contrast high-resolution magnetic resonance imaging (MRI) provides a validated and useful method to characterize carotid artery atherosclerotic plaques<sup>6</sup>. However, little is known about the usefulness of multi-contrast high-resolution MRI in HoFH patients<sup>7</sup>. We describe the use of high-resolution MRI and plaque histology in a patient with HoFH.

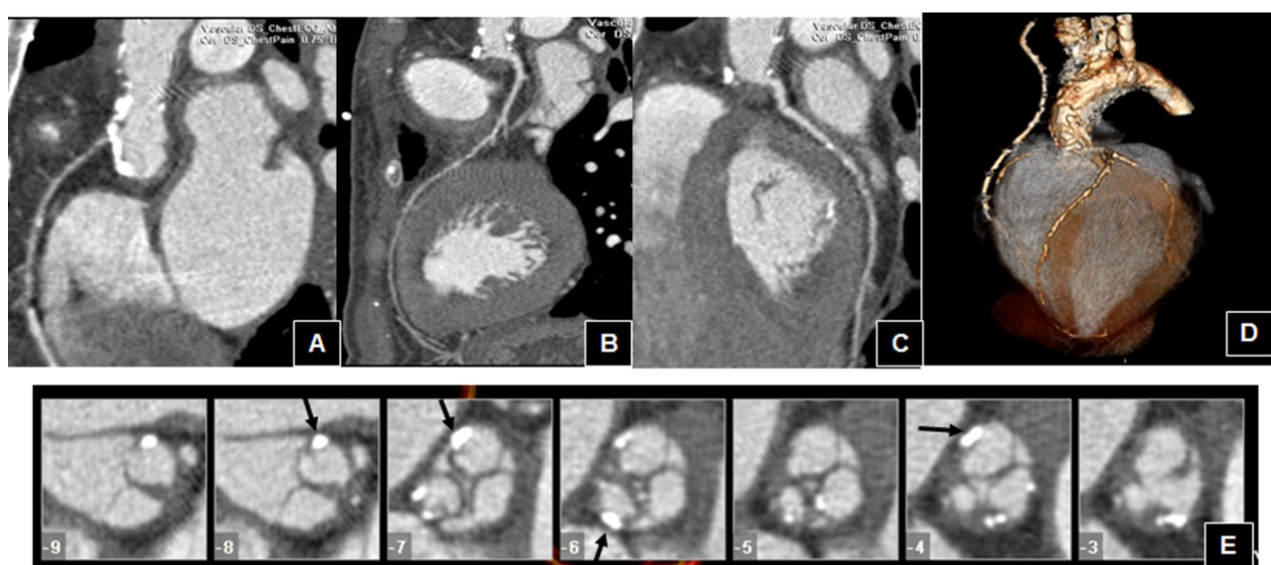
### CASE PRESENTATION

The patient was a 28-year-old woman from Beijing, China, who presented to the Neurology Clinic with intermittent blurred vision of the right eye, headache, nausea, and vomiting for the past 8 years without obvious causes. The medical history revealed that the patient already had skin and joint xanthomas at the age of one year. HoFH was suspected at the age of 3, when blood examination revealed plasma cholesterol >20 mmol/L, and hyperlipidemia was found in both parents. The patient's family could not afford genetic analysis or LDL-apheresis. After several years of conventional statin treatment, plasma cholesterol levels remained high, between 13 and 15 mmol/L. The patient underwent percutaneous coronary intervention (PCI) at the age of 12, and coronary CT angiography showed

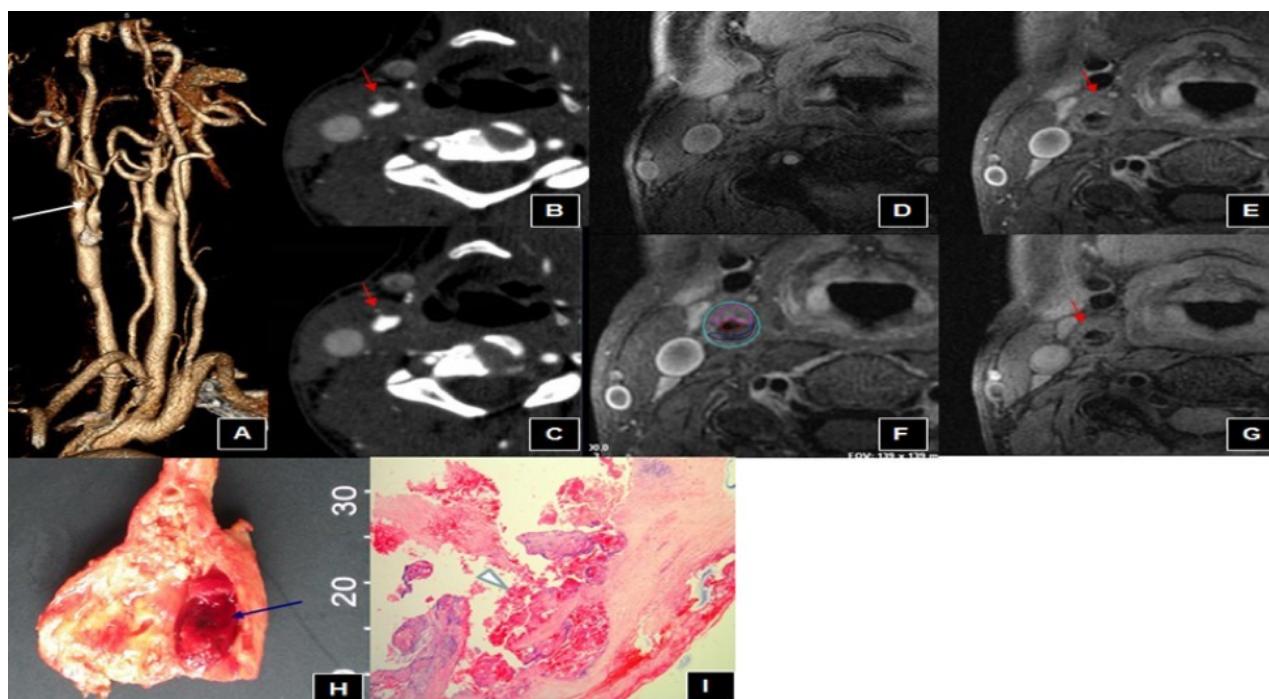
diffuse lesions in the coronary artery with more than 50% stenosis (Fig. 1 A-D) as well as calcified lesions at the aortic root and coronary artery orifice (Fig. 1 E). We suspected that the patient's current symptoms of intermittent blurred vision might be caused by carotid artery atherosclerosis.

Therefore, carotid color Doppler ultrasound, intracranial Doppler ultrasound, and carotid artery CT angiography were performed. Carotid Doppler ultrasound showed bilateral common carotid artery (CCA), internal carotid artery (ICA), and external carotid artery (ECA) wall thickening with hyperechoic signals. The bifurcation of the right CCA showed hyperechoic plaque, with a maximum plaque thickness of 4.9 mm; the lesion extended to the right ICA, with maximum stenosis of about 90%. Right ECA stenosis was 75%, while that of the left CCA, ICA, and ECA was 70%. Transcranial Doppler ultrasound showed near occlusion of the right intracranial ICA. The right ophthalmic artery had a reverse flow, with the right ECA through the ophthalmic artery reversing ICA supply, as well as posterior communicating artery opening. Carotid artery CT angiography revealed the same degree of stenosis as the ultrasound, with plate-like calcification located at the bifurcation of the right CCA, proximal ICA, and ECA (Fig. 2 A-C).

Subsequently, high-resolution multi-contrast MRI was used to further evaluate carotid plaque components and vulnerability. Imaging was performed on a 3T MRI scanner using specially-designed phased-array



**FIGURE 1.** COMPUTED TOMOGRAPHY ANGIOGRAPHY OF THE PATIENT. A-C, CALCIFIED, NON-CALCIFIED, AND MIXED PLAQUES IN THE MIDDLE AND DISTAL RCA, LAD, AND LCX; D, BYPASS FROM IMA TO RCA; E, IMAGES SHOWING CALCIFIED PLAQUES ON THE AORTIC VALVE (RED ARROWS)



**FIGURE 2.** CTA, MRI, AND HISTOLOGY OF THE RIGHT CAROTID ARTERY PLAQUE.

A, CTA showed 90% stenosis in the bifurcation of the CCA and proximal ICA (white arrow); B-C, two transverse slices of the CTA showing a low-density plaque in the R-CCA (red arrow); D-G, MR, TOF, T1W, T2W, and PD images of the R-CCA (direction and location same as in B). Red arrows indicate plaques: the pink contour shows thrombosis with an irregular surface; H, histology showed red thrombosis on the plaque surface; I, specimen analysis confirmed the rupture, subsequent thrombus formation, and calcification (arrowhead).

**TABLE 1.**

Time	Events
Initial presentation	Intermittent blurred vision of the right eye, headache, nausea, and vomiting, for the past 8 years without obvious causes.
Day 1	Transfer to ultrasound department for carotid color Doppler ultrasound, intracranial Doppler ultrasound, which showed bilateral common carotid artery (CCA), internal carotid artery (ICA), and external carotid artery (ECA) plaque with >70% stenosis. Right intracranial ICA was nearly occluded, with high resistance and low blood flow.
Day 2	Transfer to the radiology department for computed tomography carotid angiogram, which confirmed mix plaque with plate-like calcification located at the bifurcation of the right CCA, proximal ICA, and ECA. lumen stenosis >90%
Day 4	Transfer to the radiology department for high-resolution MRI. Carotid artery wall imaging showed plaque located at the right bifurcation of the CCA extended to the ICA, lumen stenosis close to occlusion, plaque surface ulcer-like with thrombosis. Lumen stenosis >90%
Day 15	Right carotid artery endarterectomy confirmed yellow fatty-like plaque with thrombosis at the bifurcation of the CCA
1 Month	Carotid color Doppler ultrasound showed normal blood flow of the right carotid artery and internal carotid artery, without lumen stenosis.
Outpatient clinic (6 months)	Marked improvement in patient's symptomatic status, no intermittent blurred vision onset

surface coils (Shanghai Chenguang Medical Technologies CO, LTD, Shanghai, China). A standardized protocol was used to obtain three different contrast-weighted images (time of flight [TOF], and T1-, T2-weighted images) of the carotid arteries 2 cm proximal and 2 cm distal to the bifurcation, respectively. MRI of the carotid showed bilateral CCA, ICA, and

ECA wall thickening, as well as diffused plaque formation. Plaque signals of the left side showed iso-intensity in TOF, T1w and T2w sequences. Calcification was reflected by hypo-intense areas located at the middle layer of the plaque, with moderate stenosis. The plaque located at the right bifurcation of the CCA extended to the ICA, causing lumen stenosis close to

occlusion. Notably, the plaque surface was irregular, showing ulcer-like changes with slightly high signals in T1w and iso-intensity in TOF and T2w sequences (Fig. 2 D-G). Based on our clinical experience, we considered these as vulnerable plaques, which may be associated with ulcers and thrombosis.

The plaque characteristics, combined with the clinical presentation of the patient, prompted us to perform right carotid artery endarterectomy. Gross histology revealed plaque components were yellow fatty-like matter; moreover, there was thrombosis at the bifurcation of the CCA, which easily dropped from the plaque. The thrombosis was about 10mm long, with an irregular surface like ulcers (Fig. 2 H). Serial cross-sections with a thickness of 10 µm or less were obtained at 0.5 mm intervals from each plaque specimen. These sections were stained with hematoxylin and eosin and examined microscopically by a pathologist blinded to the MRI results. Histology confirmed plaque rupture, subsequent thrombus formation, and calcification. Thus, the vulnerability of the plaque, which was suspected based on the MRI results, was confirmed through histologic examination. At 1-month follow-up, carotid color Doppler ultrasound showed normal flow and no lumen stenosis of the right carotid artery and internal carotid artery blood. At six months follow-up, the patient did not report a recurrence of her symptoms.

## DISCUSSION

Patients with FH are at very high risk of developing atherosclerosis at a young age. Increased carotid intima-media thickness (IMT) and carotid plaques may be apparent in FH patients already during childhood and (especially in HoFH) may lead to clinical events before reaching adulthood, as in the patient described in our case report. Carotid plaque burden may be assessed by carotid ultrasonography<sup>8</sup>. More detailed characterization of plaques in HoFH patients may be useful for risk stratification and as an outcome measure in clinical studies. However, very few studies have been done on assessing plaque composition in patients with FH, especially in HoFH<sup>9</sup>. High-resolution MRI of the carotid artery has the ability to qualitatively and quantitatively assess the main components of advanced human carotid atherosclerotic plaques in vivo and was found to correlate with findings of histologic plaques<sup>10</sup>. MRI-based quantification is accurate and reproducible and has, therefore, been used as an endpoint in clinical studies of anti-atherosclerotic therapies. However,

previous studies were mainly focused on the plaque burden in the aorta wall in asymptomatic patients with heterozygous FH by using MRI<sup>11-13</sup>. Therefore, our data on carotid plaque burden may provide some information to the patients with HoFH.

## CONCLUSION

Our case demonstrates that high-resolution multi-contrast MRI played an excellent role in identifying carotid plaque components in a patient with HoFH, which can help clinical physicians reach a diagnosis and provide an intervention earlier so as to minimize the risk of developing atherosclerotic cardiovascular disease and related complications.

### List of abbreviations

HoFH = Homozygous familial hypercholesterolemia  
 ACVD = atherosclerotic cardiovascular disease  
 PCI = percutaneous coronary intervention  
 CCA = bilateral common carotid artery  
 ICA = internal carotid artery  
 ECA = external carotid artery  
 MR = magnetic resonance  
 TOF = time of flight  
 T1w = T1-weighted  
 T2w = T2 weighted  
 IMT = intima-media thickness

### Declarations

Ethical Approval and Consent to participate

The study has been approved by the Beijing AnZhen Hospital ethics review board. The design is reasonable, data collection standardized, and the relevant rights and interests of the patients have been fully protected.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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### Competing interests

There are no conflicts of interest.

### Authors' contribution

Conception and design: Zhenjia Wang and Wei Yu. Collection and assembly of data: Zhenjia Wang and Wen Liu. Data analysis and interpretation: Zhenjia Wang, Long Jiang, and Luya Wang. Manuscript writing: Zhenjia Wang and Wei Yu. Revised the language/article and final approval of manuscript: all authors.

## RESUMO

A hipercolesterolemia familiar homozigótica, uma doença patogênica rara do metabolismo da lipoproteína intimamente relacionada com a doença cardiovascular aterosclerótica prematura, pode conduzir a uma elevada deficiência e mortalidade. A hipercolesterolemia familiar homozigótica afeta tipicamente não só a raiz aórtica, comprometendo os óstios coronários, mas também outros territórios, como a carótida, a aorta descendente e as artérias renais. Imagens de ressonância magnética multicontraste de alta resolução (RM) fornecem um método validado e útil para caracterizar quantitativamente as placas de aterosclerose da artéria carótida. No entanto, muito poucos estudos foram feitos sobre a avaliação da composição da placa em doentes com hipercolesterolemia familiar homozigótica utilizando ressonância magnética de alta resolução. Este trabalho deve avaliar o valor da ressonância magnética no acesso à doença da artéria carótida em doentes com hipercolesterolemia familiar homozigótica. Descrevemos um paciente de 28 anos de Pequim, China, que se apresentou à clínica neurológica com visão turva intermitente do olho direito, dor de cabeça, náuseas e vômitos por oito anos sem causas aparentes. Suspeitava-se de hipercolesterolemia familiar com base no histórico médico e no exame laboratorial. O ultrassom Doppler carotídeo mostrou uma artéria carótida bilateral comum, artéria carótida interna e parede da carótida externa espessando-se com sinais hiperecóticos. Posteriormente, a ressonância multicontraste de alta resolução da carótida mostrou calcificação com áreas hipointensas localizadas na camada média da placa, com estenose moderada. A placa localizada na bifurcação direita da artéria carótida comum estendia-se até a artéria carótida interna, causando estenose do lúmen próxima à oclusão. O paciente foi tratado com endarterectomia da artéria carótida direita. Em seis meses de acompanhamento, não houve recorrência dos sintomas do paciente.

**PALAVRAS-CHAVE:** Espectroscopia de ressonância magnética. Placa aterosclerótica. Espessura íntima-média da carótida. Artérias carótidas. Hiperlipoproteinemia tipo II.

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