

A case report of an acute coronary syndrome in a 10-year-old boy with homozygous familial hypercholesterolaemia

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Received 4 April 2019; first decision 30 April 2019; accepted 4 December 2019; online publish-ahead-of-print 13 January 2020

Background

Familial hypercholesterolaemia is a well-known disorder, but clinical diagnoses tend to be delayed. Acute coronary syndrome may occur in childhood.

Case summary

Our patient, a young boy with homozygous familial hypercholesterolaemia, complained of persistent chest pain at rest and suffered a non-ST-elevation myocardial infarction (NSTEMI). The diagnosis of NSTEMI was made on the basis of his clinical features, dynamic electrocardiogram changes, troponin elevation, and cardiac computed tomography findings. The patient was managed surgically by intrathoracic artery (ITA) bypass graft. During post-operative follow-up, the young patient suffered from angina pectoris from unexpected and exceptional atheroma stenosis on the ITA.

Discussion

Familial hypercholesterolaemia needs to be identified quickly in young patients and lipid lowering therapies should be started without delay.

Keywords

Case report • Homozygous familial hypercholesterolaemia • Acute coronary syndrome • LDL cholesterol

Learning points

- Homozygous familial hypercholesterolaemia is a rare disease characterized by elevated LDL cholesterol levels and a very high risk of premature atherosclerosis, in particular for patients who are LDL receptor-negative.
- Selective lipoprotein apheresis should be started as soon as possible, in combination with oral lipid lowering therapies.

Introduction

Homozygous familial hypercholesterolaemia (HoFH) is a rare autosomal co-dominant disease characterized by high plasma levels of LDL cholesterol (LDL-C), extremely high risk of premature atherosclerotic cardiovascular disease and premature death.^{1,2} Despite the genotypic variability, the severity of the HoFH phenotype mainly depends on LDL-C levels and residual LDL receptor activity. Survival in HoFH is also driven by the on-treatment levels of LDL-C.³

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Handling Editor: Gabor G. Toth

Peer-reviewers: Andras Janosi, Thomas Johnson, Lilit Baghdasaryan, and Araz Baboujian

Compliance Editor: Rahul Mukherjee

Supplementary Material Editor: Peysh A. Patel

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We report a rare case of acute coronary syndrome (ACS) in a young patient with HoFH who is LDL receptor-negative. We also describe the therapeutic challenges we encountered during management.

Timeline

Time	Events
Family history	Parents: both parents were first cousins with heterozygous familial hypercholesterolaemia Both children have homozygous familial hypercholesterolaemia
Three years prior to presentation	Appearance of xanthomas (Figure 1) LDL cholesterol (LDL-C): 802 mg/dL (20.73 mmol/L) Lipoprotein A: 124 mg/dL (4.43 μ mol/L) Genetic diagnosis
One year prior presentation	Patient put on rosuvastatin 10 mg and ezetimibe 10 mg, LDL-C 650 mg/dL (16.8 mmol/L)
Initial presentation	
Day 1	Onset of chest pain and initial assessment revealing a non-ST-segment elevation myocardial infarction Cardiac computed tomography showed mainly an occlusive plaque in the left coronary artery Troponin 1.8 μ g/L
Day 2	Transfer to specialized hospital with paediatric cardiac surgery unit
Day 3	Coronary angiography
Day 7	Bypass graft coronary surgery
Follow-up	
At 1 month	LDL apheresis started 1 month after cardiac surgery No visible symptoms
At 3 months	Angina pectoris and positive stress testing Underwent percutaneous intervention with 1 stent at left intrathoracic artery ostium

Case presentation

Patient information and physical examination

A 10-year-old boy presented to the paediatric emergency department of the tertiary cardiac centre for chest pain. Symptoms started 4 h earlier after a run. At the admission, the child complained of persistent chest pain, but no shortness of breath or syncope. He described a similar episode 5 days previous after walking for a couple of hours, but the symptoms disappeared spontaneously.

Physical examination revealed a boy in relatively good health: 37 kg, blood pressure of 165/82 mmHG, heart rate of 71 b.p.m., and



Figure 1 Xanthomas.

body temperature of 36.6°C. There was no congestive heart failure, pulmonary auscultation was unremarkable, and cardiac auscultation found regular pulse and no heart murmur. He did not have a rash or any symptoms of joint pain. Ganglionic areas were free. Cutaneous inspection revealed cutaneous and tuberous xanthomas on the patient's elbows, wrists, knees, and feet (Figure 1).

Indeed a genetically diagnosed true HoFH (classified LDL receptor-negative/negative due to identical null mutations on LDL receptor) was known since about 3 years. Unfortunately, LDL apheresis has not been proposed as treatment at time of genetic diagnosis and the patient only received a combination of rosuvastatin 10 mg and ezetimibe 10 mg, oral treatment started 1 year before the ACS.

The LDL-C level at admission was 615 mg/mL (15.9 mmol/L) on rosuvastatin–ezetimibe combination therapy.

Diagnostic assessment

ST-segment depression in leads V4–V6 was observed on electrocardiogram (ECG) (Figure 2). Maximum serum troponin was 2.2 μ g/L (normal < 0.1 μ g/L), suggestive of a non-ST-elevation myocardial infarction (MI). Emergency echocardiography showed no significant abnormalities. Left ventricular ejection fraction (LVEF) was estimated as 60% with normal wall motion.

A dual source 126-slice cardiac computed tomography (CT) showed a critical (near occlusive) non-calcified plaque at the distal end of the left main coronary artery, immediately before a trifurcation (Figure 3). Another lesion was found on right coronary ostium with more than 90% stenosis (Figure 4). Severe atheroma on both the aortic root and arch were diagnosed.

Interventions

After consultation with the care team, the patient was transferred to a specialized hospital centre with a paediatric cardiac surgery unit where coronary angiography was performed. Cardiac CT findings were confirmed (Figures 5 and 6). As the atheroma affected all three major epicardial territories, it was agreed that surgical revascularization was the preferred treatment strategy. Bilateral internal thoracic artery (ITA) bypass grafts were performed 'off-pump', with the right

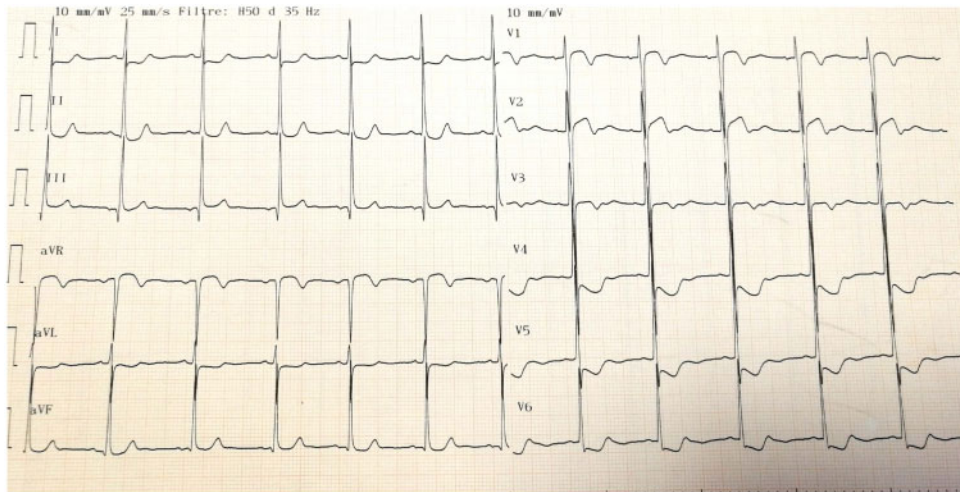


Figure 2 Non-ST-elevation myocardial infarction patterns in the 12-lead electrocardiogram.

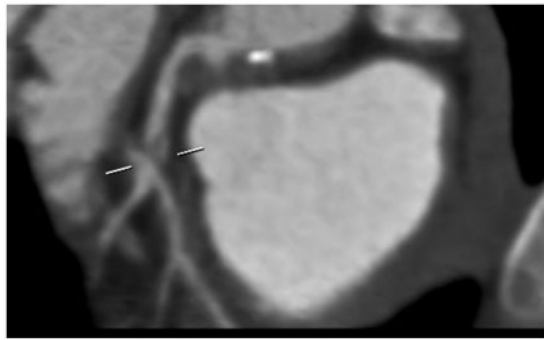


Figure 3 Non-calcified plaque is shown at the distal portion of left main coronary with more than 90% stenosis.

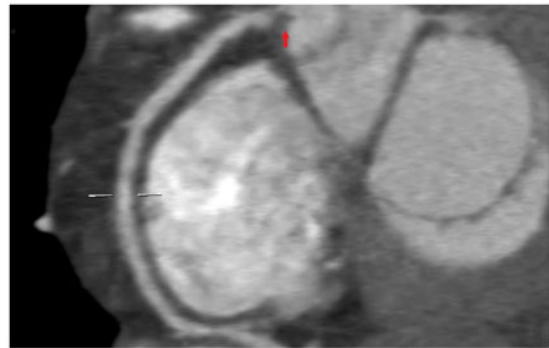


Figure 4 Non-calcified plaque is shown at the ostium of right coronary with more than 90% lumen stenosis.

ITA to right coronary artery and the left ITA to left anterior descending artery (LAD). Post-operative care went well, and the child was sent home to wait for lipoprotein apheresis.

Follow-up and outcomes

At 6 weeks of follow-up, the patient was asymptomatic with no post-operative complication. Echocardiography results were normal for LVEF and normal wall motion. The sinus rhythm was normal with a normal ST-segment on 12 leads.

LDL apheresis was started 1 month after acute MI. The first session reduced LDL-C from 11.62 to 3.89 mmol/l.

Three months after surgery, the child complained of chest pain during swimming lessons at school. He was brought in to do cycle ergometer stress testing: the ECG revealed 3 mm ST-segment depression in leads V4–V6 at 50 W (protocol: 10 W/min). The care team sent him to a specialized hospital centre for coronary angiography to assess ITA bypass graft permeability. One stenotic lesion

was found on the left ITA ostium. A 3 mm stent was implanted to achieve revascularization.

Four weeks after left ITA stenting, the child had another successful LDL apheresis session, and weekly LDL apheresis sessions were sustained. The coronary angiography team recommended a stress echocardiography at 3 months for the next follow-up in order to avoid more exposure to radiation. He performed 50 W doing cycle ergometer stress testing: the ECG revealed normal ST-segment on 12 lead and echocardiography showed normal wall motion. Heart rate reached 70% of maximum theory heart rate.

Discussion

The first challenge is relative to treatment for an ACS in a young boy: cardiac CT is a non-invasive test with a good predictive negative value (95–100%) and diagnostic accuracy (95%).⁴ In this case, the patient received 80 mg of Nadolol 1 h before the exam to obtain the best

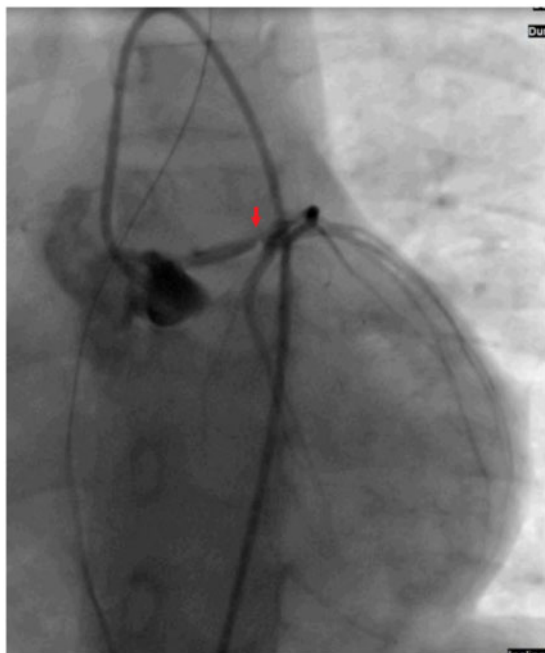


Figure 5 Coronary angiography showing the critical stenotic lesion at the distal portion of left main coronary.

ECG-gating. Although cardiac CT is not recommended to rule out ACS, after discussion with coronary angiography team and heart surgery team, we agree to avoid a high risk invasive coronary angiography in a centre without a paediatric cardiac surgery unit. Hopefully, the dual source 126-slice cardiac CT performed diagnosis of subocclusive lesions. Nonetheless, we were not able to differentiate chronic subocclusive lesion from plaque rupture. Furthermore, coronary angiography would show LAD lesion as plaque rupture and right coronary lesion as chronic subocclusive lesion.

Coronary bypass graft surgery is particularly complex for child patients.⁵ Furthermore, outcomes in short- and long-term follow-up are well known for Kawasaki patients but there is few data for plaque rupture MI in childhood. ITA bypass graft is the strategy of choice and has better outcomes than autologous saphenous vein graft. The main issue after ITA surgery is flow competition, but this problem is logically more frequent in Kawasaki disease than coronary atheroma disease.

The second challenge is the difficulties with recognizing HoFH and instigating treatment early. Recent genetic studies of HoFH have highlighted the great variability of clinical phenotypes.^{2,6} Indeed, HoFH is either caused by homozygosity or compound heterozygosity for mutations in the three major genes for LDL receptors, apolipoprotein B, and proprotein convertase subtilisin–kexin type 9 (PCSK9). The genetic heterogeneity in HoFH underlies the phenotypic variability. The severity of the clinical phenotype is directly related to the levels of LDL-C and depends mainly on residual LDL receptor activity.⁷

Untreated HoFH patients who are LDL receptor-negative rarely survive beyond their twenties⁸ due to accelerated atherosclerosis,

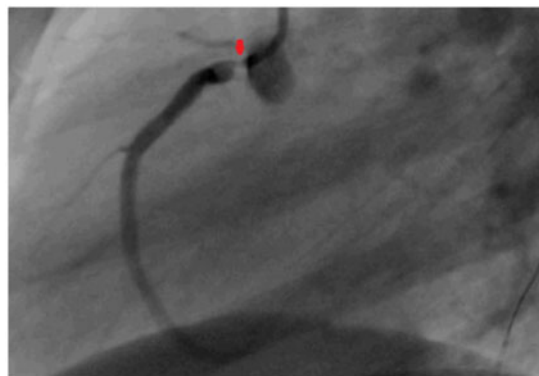


Figure 6 Coronary angiography showing the subocclusive lesion in the right ostium.

which results in valvular and supravalvular aortic stenosis and coronary stenosis. We reported a typical example of the most severe type of HoFH: the young boy is LDL receptor-negative with a very high baseline LDL-C level (>800 mg/dL, >20 mmol/L). He had been taking a combination of rosuvastatin and ezetimibe since the age of 7 years. Certainly, treatment with statin and statin plus ezetimibe has improved the survival for patients with HoFH.^{8,9} However, the response to rosuvastatin is less for LDL receptor-negative HoFH patients,¹⁰ and the complementary LDL-C decrease observed by the combination of ezetimibe to statin therapy remains modest.¹¹ Our case confirms the low response to this combination of therapies. Moreover, the efficacy of PCSK9 inhibitors such as evolocumab has only been observed for HoFH patients with residual LDL receptor activity.¹² Finally, newer medications like lomitapide or mipomersen are not suitable for patients at a very young age. Consequently, selective lipoprotein apheresis continues to be the best therapeutic option, particularly for patients with HoFH who are LDL receptor-negative.^{1,2}

The reported case is an illustration of the therapeutic challenge for LDL receptor-negative HoFH. For this category of individuals, the recommendation is to consider weekly lipoprotein apheresis from the age of 2 and no later than 8, combined with maximum the tolerated dose of statins and ezetimibe.¹³

Unfortunately, the severity of HoFH is not well known by medical community and in particular, the rare cases of patients with an absence of LDL receptors due to null–null mutations should be addressed as soon as possible to a specialized lipid clinic. In the present case, the treatment option by LDL apheresis was never discussed before the acute event, as well as for his sister also diagnosed with HoFH. This situation illustrates the need to refer all the family members in a lipid clinic for full family screening and therapeutic decisions.

Finally, the importance of family screening as a systematic evaluation of the other family members was needed: the parents are both heterozygous FH and the 8-year-old sister, who has the same homozygous disease, is also a candidate for lipoprotein apheresis.

Conclusion

We report a rare case of MI in a 10-year-old boy with HoFH. Physicians should be able to identify xanthomas and make the association with severe aortic root and coronary atherosclerosis risk seeing as early diagnosis and treatment can prevent premature death due to MI. Furthermore, cardiac CT is a modern and safe strategy to assess coronary stenosis in hospitals without a cardiac paediatric surgery unit. Finally, surgical treatment remains the strategy of choice, despite the unexpected appearance of a stenotic lesion in this case.

Lead author biography



Thibault Leclercq is a Cardiology PhD specialized in cardiovascular imaging. He actually practices echocardiography, cardiac CT, MRI cardiac, cardiac SPECT, and stress echocardiography as well. He keeps doing clinician activities as ICU and consultation activities.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Acknowledgements

The authors are grateful to Suzanne Rankin for the English review of the manuscript.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: M.F. has received grants, consulting fees and/or honoraria, and delivering lectures for Abbott, Akcea/Ionis, Amgen, AstraZeneca, Eli Lilly, Kowa, Merck and Co, Mylan, Pfizer, Roche, Sanofi/Regeneron, and Servier. R.M. has received grants from NHS Novalac et Nestlé Science Science. All other authors declared no conflict of interest.

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