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CORONARY, PERIPHERAL, AND STRUCTURAL INTERVENTIONS

CASE REPORT: CLINICAL CASE

Acute Coronary Syndrome in a 9-Year-Old Girl With Homozygous Familial Hypercholesterolemia

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ABSTRACT

Familial hypercholesterolemia (FH) is a prevalent and underrecognized disorder. A young girl with previously undiagnosed homozygous FH presented with acute coronary syndrome. Severe coronary ostial stenosis and severe supravalvular aortic stenosis from atheromatous plaque was discovered. This case highlights the importance of screening and timely diagnosis of FH. (JACC Case Rep 2024;29:102417) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

The patient is a previously healthy 9-year-old girl of Arab ethnicity who presented to the emergency department (ED) with a 7-day history of progressive exertional chest pain and diaphoresis. In the week prior to presentation, she was evaluated 3 times in outpatient and ED settings. Initially, she was noted to have a new cardiac murmur and a screening lipid panel showed low-density lipoprotein (LDL) of 731 mg/dL. At that time, outpatient follow-up with pediatric cardiology was recommended. She returned to the ED a third time on day 7 by ambulance with symptoms of severe chest pain at rest, diaphoresis, and an ashen appearance with minimal exertion.

On arrival, she was afebrile, tachycardic, and normotensive. Physical examination revealed a loud systolic murmur, best heard at the right upper sternal border. She had no other significant physical examination findings, including no tendon xanthomas or corneal arcus.

LEARNING OBJECTIVES

- To recognize acute coronary syndrome in children and young adults presenting with exertional symptoms.
- To advocate for family screening and education to identify and treat patients with familial hypercholesterolemia.
- To emphasize the role of novel therapeutic treatments for managing HoFH.

PAST MEDICAL HISTORY

The patient had no significant past medical history. The parents were consanguineous, first cousins who had recently emigrated from Iraq. Known family

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ABBREVIATIONS AND ACRONYMS

ED = emergency department

FH = familial hypercholesterolemia

HoFH = homozygous familial hypercholesterolemia

LDL = low-density lipoprotein

LMCA = left main coronary artery

LVOTO = left ventricular outflow tract obstruction

RCA = right coronary artery

SVAS = supravalvular aortic stenosis

history was significant for hyperlipidemia in her mother and cardiac arrest in her paternal grandmother at 40 years of age (Figure 1). Her father's lipid levels were unknown at the time of presentation.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for young patients with exertional chest pain includes left ventricular outflow tract obstruction (LVOTO), coronary artery anomalies, pericarditis, myocarditis, cardiomyopathy, ruptured sinus of Valsalva aneurysm, aortic root dissection, tachyarrhythmia, coronary artery disease secondary to Kawasaki disease, and atherosclerosis secondary to familial hypercholesterolemia (FH).

INVESTIGATIONS

High-sensitivity troponin level at presentation was 2,090 ng/L, and brain natriuretic peptide level was 137 pg/mL. Her initial lipid panel showed a total cholesterol level of 802 mg/dL, LDL level of 731 mg/dL, triglyceride level of 123 mg/dL, and high-density lipoprotein level of 46 mg/dL. Electrocardiogram showed normal sinus rhythm with ST-segment depressions in V_3 to V_6 and nonspecific T-wave changes in leads III and aVF (Figure 2).

Transthoracic echocardiography showed mild concentric left ventricular hypertrophy with mild basal wall hypokinesis and normal ejection fraction. A trileaflet aortic valve with thickened leaflets, supravalvular aortic stenosis (SVAS), and mild aortic insufficiency was seen (Figure 3). The origin of the left main coronary artery (LMCA) appeared mildly stenotic with flow acceleration.

Coronary angiography was performed on the second day of admission to delineate anatomy, degree of stenosis, and aid in surgical planning. A 2 coronary artery system was seen with retrograde filling of the right coronary artery (RCA). There was severe ostial stenosis of the LMCA (Figure 4). The LMCA, left anterior descending artery, and circumflex coronary artery all had a normal course without stenosis. The RCA was severely diminutive with near-total occlusion at the origin.

Genetic testing confirmed the diagnosis of homozygous familial hypercholesterolemia (HoFH). Molecular genetic testing showed 2 pathogenic variants, c.2413G>C (p.Gly805Arg) (homozygous), in *LDLR*. Cascade screening confirmed heterozygous FH with 1 pathogenic variant of c.2413G>C (p.Gly805Arg) in *LDLR* in each parent. Lipid screening in parents showed LDL levels of 395 and 185 mg/dL, in father and mother, respectively.

MANAGEMENT

She received immediate treatment with a statin, aspirin, and a heparin drip followed by urgent lipid apheresis on the day of admission. On day 3 of

FIGURE 1 Pedigree

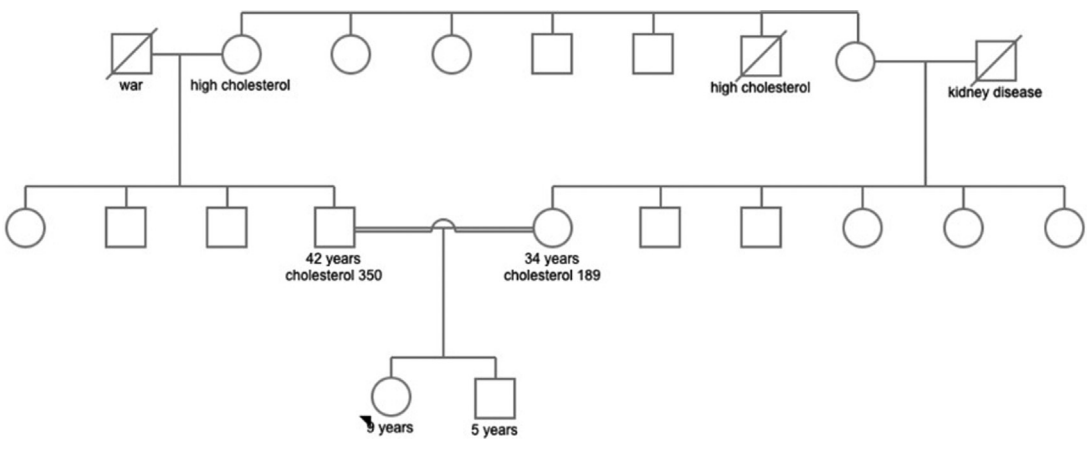
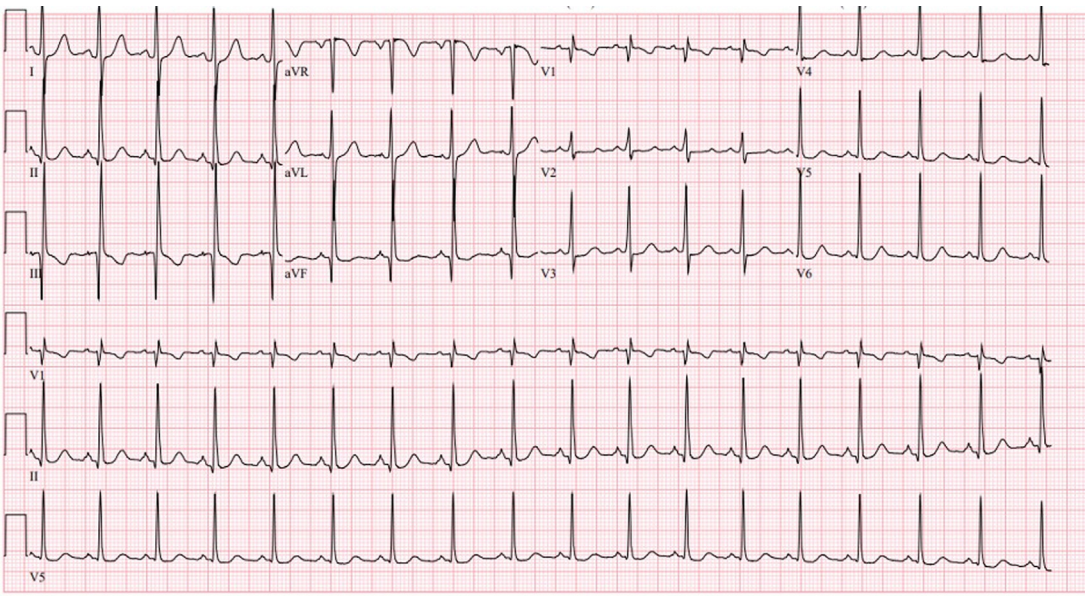


FIGURE 2 **Electrocardiogram**



Electrocardiogram showing sinus rhythm with ST-segment depressions in leads V_3 to V_6 and nonspecific T-wave changes in inferior leads.

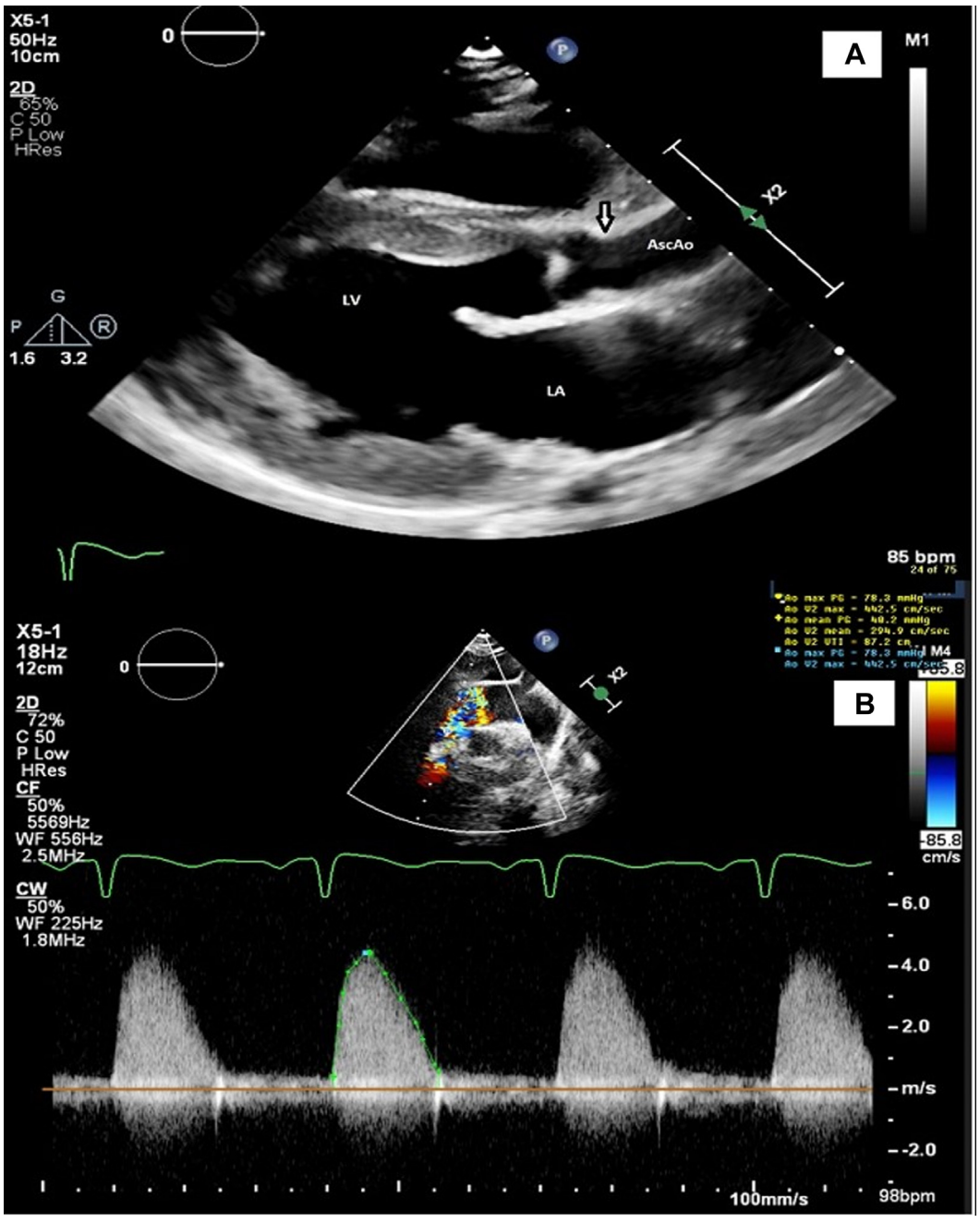
admission, she went to the operating room to address her SVAS and coronary ostial stenosis. Intraoperative findings included severe atherosclerosis of the ascending aorta and aortic root causing severe SVAS (**Figure 5**) and thickened aortic valve leaflets. The RCA origin was occluded, with diffuse narrowing (1 mm in size) beyond its origin. There was severe narrowing of the LMCA with post-stenotic dilation and atherosclerosis at its origin. Soft atherosclerotic plaques were noted at the origin of the left anterior descending and circumflex arteries. She underwent the Ross procedure, left main coronary artery augmentation, and reimplantation of the right coronary artery to the neo-aortic root. Postoperative transthoracic echocardiogram showed normal biventricular function and no gradient across the LVOTO. Her postoperative course was uneventful. She was initiated on multiple lipid-lowering medications including atorvastatin, ezetimibe, and evolocumab, with an additional plasmapheresis procedure prior to discharge. Her LDL level at discharge was 199 mg/dL. She was discharged home 9 days after surgery with a plan to undergo plasmapheresis every 2 weeks as an outpatient.

DISCUSSION

FH is a prevalent but underdiagnosed disorder of lipoprotein metabolism characterized by markedly elevated plasma LDL levels from birth. Most mutations are found in the *LDLR*, *APOB*, *PSK9*, and *APOE* genes. The identified mutation in this patient, c.2413G>C (p.Gly805Arg) in *LDLR*, is rare, with limited reports in databases (ClinVar ID 440694). It causes a missense change that reduces the amount of precursor *LDLR* in the endoplasmic reticulum, thereby reducing the number of membrane-bound *LDLR* molecules for LDL-cholesterol clearance.[1]

HoFH is rare, with an estimated prevalence of approximately 1 in 300,000 cases compared with heterozygous FH, which has a worldwide prevalence of about 1 in 300 individuals.[2] Patients with HoFH develop accelerated atherosclerosis, often leading to clinical consequences manifesting in childhood, as seen in the highlighted case. Sudden death has been reported in children as young as 4 years of age.[3] Cholesterol deposition in the aortic root leading to coronary ostial stenosis and SVAS is typical cardiac manifestations in childhood and adolescence.[4]

FIGURE 3 Transthoracic Echocardiogram

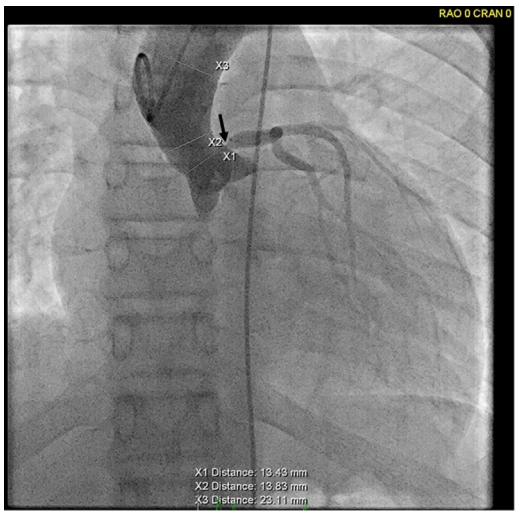


Transthoracic echocardiogram images showing combined valvular and supravalvular aortic stenosis (arrow) (A) with a peak gradient 78 mm Hg and mean gradient 40 mm Hg (B).

SCREENING AND AWARENESS. Current guidelines recommend lipid screening starting at 2 years of age with a family history of premature atherosclerosis, and universal lipid screening at 9 to 11 years of age.[5]

Despite a positive family history, the patient and her parents were unaware of their genetic diagnosis and risk of premature morbidity and mortality. In patients with FH, early identification and

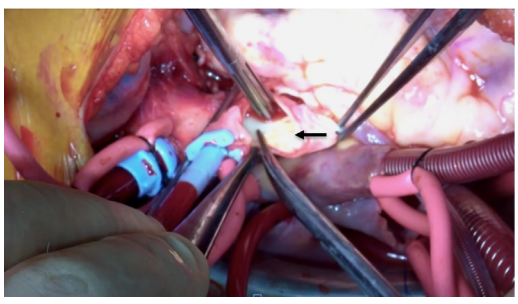
FIGURE 4 Aortic Root Angiogram



Aortic root angiogram showing severe left main ostial stenosis (arrow) and near-total occlusion at right coronary artery origin with supravalvar narrowing (X1).

intervention is critical to improving outcomes. Limited progress has been made despite repeated calls to action from the international FH community and World Health Organization. This case highlights the importance of diagnosis, treatment, family screening, and education for generations of affected family members.

FIGURE 5 Intraoperative Findings



Intraoperative findings of large atheromatous plaque above the sinotubular junction of the aorta (arrow) causing severe supravalvar aortic stenosis.

EMERGING THERAPIES. Cholesterol-lowering therapies have significantly improved survival in patients with HoFH. Statins and plasmapheresis are the mainstays of treatment and have doubled survival in the last several decades.[4] Novel lipid-lowering therapies have improved the management of HoFH and reduced annual rates of major atherosclerotic cardiovascular events. Lomitapide, an oral inhibitor of microsomal triglyceride transfer protein, reduces LDL levels by 60%; however, concerns persist regarding hepatic steatosis despite its efficacy.[2] Evinacumab, a monoclonal antibody that inhibits angiopoietin-line protein 3, has been used in adolescents without any adverse effects, leading to significant improvement in LDL levels and decreased frequency of apheresis.[6] In March 2023, it was Food and Drug Administration approved for use in children as young as 5 years of age with HoFH. Emerging therapeutic avenues, such as angiopoietin-line protein 3 blockade using small interfering RNA therapies, gene transfer, and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-based gene editing, show promise.[2] The long-term benefit of novel therapeutics in the pediatric population is yet to be determined; however, initial results are promising.

FOLLOW-UP

The patient was followed in the pediatric lipid clinic, and her medical management was optimized on atorvastatin, ezetimibe, and evolocumab with plasmapheresis every 2 weeks. Her LDL levels on this regimen were 110 to 130 mg/dL. Five months after her initial presentation, she received her first infusion of evinacumab. She had a robust initial response and her 2-week post-treatment LDL level was 60 mg/dL. Her most recent LDL level was 45 mg/dL, 9 months after her initial presentation. Her echocardiogram shows no LVOTO with patent coronary ostia by color flow mapping.

CONCLUSIONS

This report highlights the importance of suspecting acute coronary syndrome in pediatric patients with exertional symptoms and cardiac physical examination findings, particularly in the setting of severely elevated LDL levels. The case emphasizes the importance of promptly identifying individuals with FH and cascade screening within affected families to prevent premature atherosclerosis and increase the likelihood of event-free survival. Novel therapeutics have the potential to revolutionize the treatment of HoFH.

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