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CASE REPORT

CLINICAL CASE

Supravalvular Aortic Stenosis in Homozygous Familial Hypercholesterolemia: Contemporary Management

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ABSTRACT

We report a case of a patient diagnosed with homozygous familial hypercholesterolemia and progressive supravalvular aortic stenosis. Treatment with long-term low-density lipoprotein apheresis and management with novel lipid-lowering agents including an angiopoetin-like protein inhibitor led to significant low-density lipoprotein reduction. The case highlights the challenges in managing the manifestations of homozygous familial hypercholesterolemia. (J Am Coll Cardiol Case Rep 2024;29:102342) © 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

This case involves a 47-year-old woman with clinical homozygous familial hypercholesterolemia (HoFH) and progressive supravalvular aortic stenosis (SVAS).

LEARNING OBJECTIVES

- To understand the clinical manifestations associated with HoFH including SVAS.
- To recognize the diagnostic criteria for HoFH, including genetic and clinical parameters.
- To evaluate the role of novel lipid-lowering strategies, such as LDL apheresis, ACYL inhibitors, microsomal triglyceride transport protein inhibitors, and angiopoietin-like protein 3 inhibitors, in the management of HoFH.

At 27 years of age, she presented with angina and was found to have multivessel coronary artery disease (CAD). Subsequently, she underwent 2-vessel coronary artery bypass grafting (CABG) with the use of bilateral internal mammary grafts to the left anterior descending and right coronary arteries.

Post-CABG, she participated in cardiac rehabilitation. Given her low-density lipoprotein cholesterol (LDL-C) level of 500 mg/dL, the patient was referred to preventative cardiology at a national referral center for genetic lipid disorders and a site for the national familial hypercholesterolemia (FH) registry. Our patient declined genetic testing for HoFH but met clinical criteria for an HoFH diagnosis. She has been trialed on numerous lipid-lowering therapies (**Figure 1**) including rosuvastatin 40 mg, niacin 1,000 mg and 2,000 mg, and colesevelam 625 mg, as well as novel therapies such as alirocumab 75 mg, lomitapide 20 mg, bempedoic acid 180 mg,

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ABBREVIATIONS AND ACRONYMS

AV = aortic valve

CABG = coronary artery bypass graft

CAD = coronary artery disease

HoFH = homozygous familial hypercholesterolemia

LDL-C = low-density lipoprotein cholesterol

MTAR = mean time-averaged reduction

SVAS = supravalvular aortic stenosis

evanicumab 15 mg/kg infusions, and LDL apheresis therapy.

One year after CABG surgery, an echocardiogram revealed mild aortic stenosis. Ten years later, at 38 years of age, a repeat echocardiogram showed SVAS with a peak aortic valve (AV) outflow velocity of 4.70 m/s, peak gradient of 88 mm Hg, mean gradient of 50 mm Hg, AV area of 0.67 cm^2, and normal ejection fraction.

At 44 years of age, she underwent a coronary computed tomography angiography to investigate the anatomy of her AV and SVAS, which showed a trileaflet AV with calcification on the left coronary cusp. The right and noncoronary cusps were normal. The study showed SVAS 6 mm distal to the annulus secondary to a near-occlusive atherosclerotic plaque extruding intraluminally from the ascending aortic wall just above sinotubular junction (Figures 2 to 4).

Currently, she engages in daily walks exceeding 1 hour without any syncope, angina, or dyspnea. Her physical examination revealed blood pressure of 104/58 mm Hg, corneal arcus, xanthelasmas, thickened Achilles tendons bilaterally, and a 3/6 late-peaking crescendo-decrescendo systolic murmur at the base with an audible S2.

PAST MEDICAL HISTORY

In addition to CAD, her history includes stable peripheral vascular and carotid artery disease. Family history is notable for a sister and father who passed away at a young age due to CABG complications. Her mother suffered an early myocardial infarction at an unknown age.

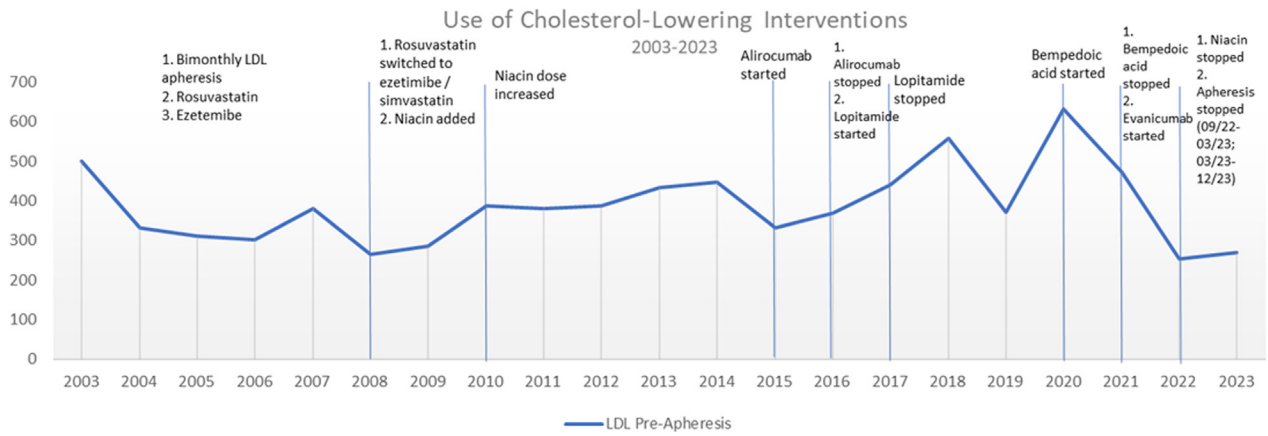
DIFFERENTIAL DIAGNOSIS

Given her severe hypercholesterolemia, corneal arcus, SVAS, xanthelasmas, premature CAD, and family history, HoFH is the most likely diagnosis. SVAS can also be associated with genetic diseases such as familial SVAS and Williams-Beuren syndrome.[1] The clinical signs of Williams-Beuren syndrome were not observed in our patient. Secondary causes of hypercholesterolemia, such as hypothyroidism, nephrotic syndrome, and cholestasis, were not present.

INVESTIGATIONS

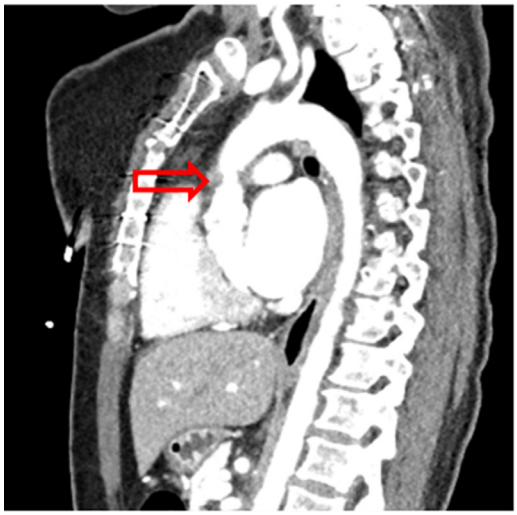
A recent echocardiogram revealed that the peak AV outflow velocity increased to 6 m/s with a peak gradient of 143 mm Hg and a mean gradient of 85 mm Hg. Left ventricular function remained normal.

FIGURE 1 Cholesterol Levels and Treatments, 2003-2023



Graph shows low-density lipoprotein cholesterol (LDL-C) levels (mg/dL) pre-apheresis on a yearly basis, rather than biweekly, for visual ease. Decrease in LDL-C levels from 2018-2019 without additional therapy may be due to patient's improved adherence to medication. LDL = low-density lipoprotein.

FIGURE 2 Sagittal View of Supravalvular Aortic Stenosis on Coronary Computed Tomography Angiography



Arrows highlight the stenotic area of the aorta (17 mm in diameter) above the aortic valve at the sinotubular junction.

Previously measured lipoprotein(a) and homocysteine levels were normal.

MANAGEMENT

Current therapy includes ezetimibe 10 mg/simvastatin 40 mg, biweekly LDL apheresis, and evinacumab 15 mg/kg infusions. Because of previously suboptimal LDL-C levels, she had been treated in the past with novel lipid-lowering agents including lomitapide, bempedoic acid, and evinacumab. Lomitapide and bempedoic acid were discontinued due to side effects. Per patient preference, apheresis was paused twice but has since resumed. LDL apheresis resulted in acute decreases in LDL-C of up to 70% with a mean time-averaged reduction (MTAR) of 25% to 30%. The addition of evanicumab alongside ezetimibe, statin, and apheresis therapy, resulted in the most substantial reduction in LDL-C with an MTAR of approximately 35% to 40% (**Figure 5**).

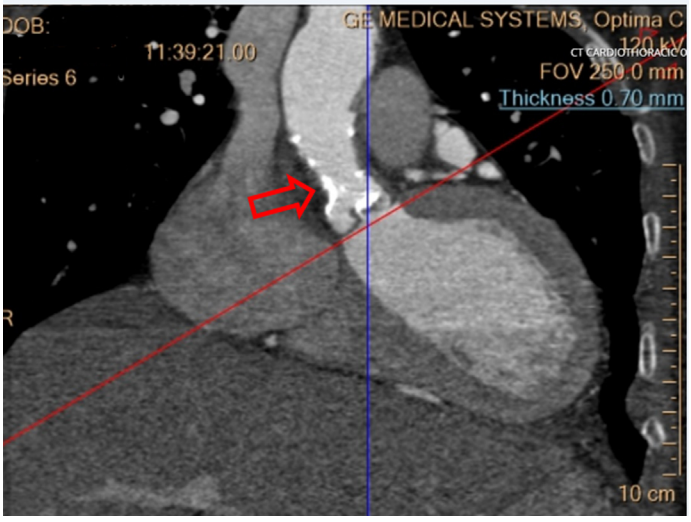
For management of SVAS, the increase in peak and mean AV gradients prompted consultation with a thoracic aortic surgical specialist. Given her young age, supravalvular predominance, and normal motion of 2 of her 3 AV leaflets, she was offered a complex reoperative aortic root replacement with annular enlargement. The patient has deferred surgery until symptoms develop.

DISCUSSION

HoFH is a rare genetic disorder most commonly caused by a loss-of-function mutation in the LDL receptor (*LDLR*) gene (85% to 90% of cases) and less commonly by variants in apolipoprotein B (*APOB*) gene (5% to 10%), proprotein convertase subtilisin-kexin type 9 (*PCSK9*) gene (1% to 3%), or low-density lipoprotein receptor adaptor protein 1 (*LDLRAP1*) gene (<1%).[2] HoFH is diagnosed genetically by pathogenic/likely pathogenic variants in the above genes. If genetic testing is unavailable or declined, HoFH can be diagnosed clinically by an LDL level >400 mg/dL in addition to xanthomas before 10 years and/or untreated LDL levels consistent with heterozygous FH in both parents.[3]

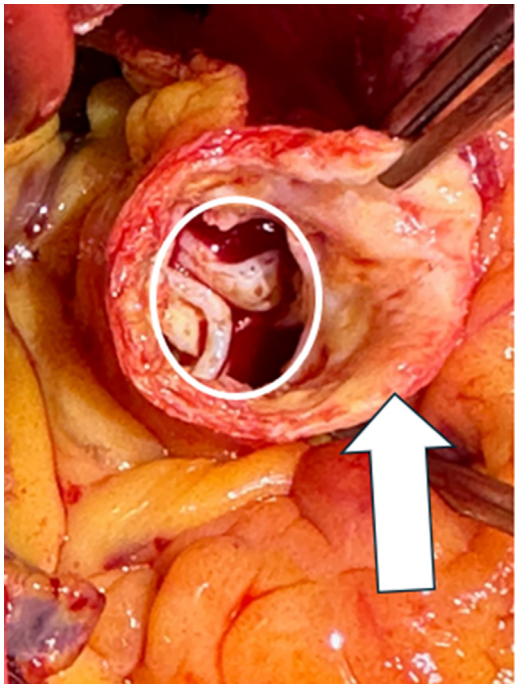
If left untreated, most patients with HoFH will die before 30 years of age due to extensive atherosclerosis.[4] Timely detection, coupled with lifestyle modifications and pharmacologic therapy, is crucial to managing atherosclerotic burden. Treatment is

FIGURE 3 Coronal View of Supravalvular Aortic Stenosis on Coronary Computed Tomography Angiography



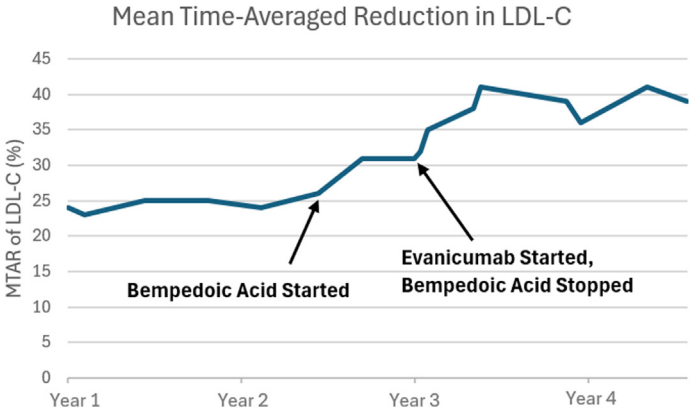
Arrows highlight the stenotic area of the aorta (17 mm in diameter) above the aortic valve at the sinotubular junction.

FIGURE 4 View of Supravalvular Aortic Stenosis During Aortic Repair (Separate Patient)



Gross image of supravalvular aortic stenosis in a separate patient with homozygous familial hypercholesterolemia. There is a calcified aortic valve (circle) with atherosclerosis extending into the aorta (arrow) decreasing the intima diameter (not visualized).

FIGURE 5 Mean Time-Averaged Reduction in LDL-C From 2019 to 2023



LDL-C reduction percentages with the addition of bempedoic acid and evanicumab, indicating greater reduction with these therapies compared to previously. MTAR = mean time-averaged reduction; other abbreviation as in Figure 1.

complicated as there is limited LDL receptor activity in HoFH, making the use of statins and *PCSK9* inhibitors (evolocumab/alirocumab) only moderately effective.[5] Thus, biweekly LDL apheresis is the standard of care. Novel lipid-lowering agents such as lomitapide (microsomal triglyceride transport protein inhibitor), bempedoic acid (adenosine triphosphate-citrate lyase inhibitor) and evanicumab (monoclonal antibody against angiopoietin-like protein 3) have shown to be effective in further lipid-lowering in HoFH patients.[4,6]

Since the introduction of statins, the risk of developing SVAS in HoFH has decreased by 95%, with an estimated prevalence of 4% of HoFH patients.[7] Patients who develop SVAS exhibit an elevated risk of premature death compared to those without SVAS.[8] Because of limited data, the optimal treatment plan for SVAS remains expert dependent. Existing studies on treatment for SVAS primarily involve children with Williams-Beuren syndrome, showing favorable long-term outcomes of surgery.[9] A single case series has been reported on SVAS repair in HoFH. Both patients underwent successful aortic root replacement with no complications at 2- and 3-years postoperation.[10]

FOLLOW-UP

This patient continues to receive biweekly LDL apheresis and monthly evanicumab infusion. Her most recent post-apheresis LDL-C level was 106 mg/dL.

CONCLUSIONS

This case underscores the complexity in managing cardiovascular complications of HoFH. The patient's unique clinical profile, including severe hypercholesterolemia, premature CAD, difficult lipid-lowering management, and SVAS highlights the importance of implementing a combination of specialized treatment approaches. Regular follow-up with ongoing investigation and collaboration remains crucial in optimizing care for rare genetic disorders such as HoFH.

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