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Young onset valvular dysfunction as a presentation of familial hypercholesterolemi a due to LDL receptor mutation and transient response to LDL apheresis

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INTRODUCTION

Familial hypercholesterolemia is a genetic disorder causing elevated LDL cholesterol levels. It affects 1 in 250 people worldwide, with homozygous FH being the more severe form. HoFH leads to extremely high LDL cholesterol, increased risk of premature cardiovascular disease, and aortic stenosis. Recent data from over 7 million individuals worldwide have updated the prevalence estimates of FH. The prevalence of HeFH is now estimated at 1 in 311, higher than previously thought. The persistent and markedly elevated levels of LDL-C in HoFH contribute to the accelerated deposition of cholesterol in the aortic valve, promoting calcification and stenosis. If left untreated, survival beyond age 30 was rare, but advancements in medical care have improved survival rates. With advancements in medical care, clinicians now observe survival beyond 50 years with increasing frequency in developed countries. Early diagnosis and management are critical to improve patient outcomes and survival in HoFH cases.

PRESENTATION OF CASE and PROCEDURE DETAILS

A 5-year-old girl presented with multiple skin lesions over her ankles, knees, elbows, and eyelids, prompting consultation and a lipid profile, which revealed a dangerously high LDL of 392 mg/dl. Further cardiac evaluation showed severe aortic stenosis with moderate aortic regurgitation, but no symptoms of chest pain. She was diagnosed with familial hypercholesterolemia (FH) after genetic testing confirmed a mutation in the LDL receptor gene. Despite treatment with atorvastatin, ezetimibe, and later niacin, her LDL levels remained very high, peaking around 600-700 mg/dl. She underwent surgery for aortic stenosis with aortic valve replacement along with aortic root augmentation. After aortic valve replacement surgery, she continued on statins, ezetimibe, and niacin, with brief use of the PCSK9 inhibitor evolocumab, which was discontinued due to cost and limited efficacy. She was advised to consider LDL apheresis but was reluctant. Later she was lost to follow-up. Over last two years, new atypical skin lesions appeared, and her lipid profile remained poorly controlled. She returned for follow-up and was once again counseled about LDL apheresis

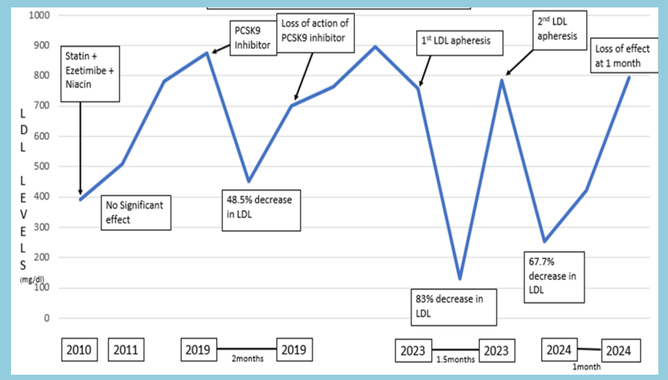

Figure 2: Trajectory of LDL over time with various interventions

A Cascade Filtration (CF) plasmapheresis was performed using plasma fractionator (Evaflux 5A20, Kawasumi Laboratories Inc. Tokyo, Japan) with cell separator Spectra Optia (Terumo BCT, Lakewood, CO, USA) to extract plasma, removing atherogenic components like LDL while retaining HDL and albumin. The patient's blood volume was 3.5 liters, and 2.5 times the plasma volume was processed. The procedure used acid citrate dextrose A as an anticoagulant, with calcium gluconate given to manage hypocalcemia. No complications or adverse events occurred during the process.

MANAGEMENT

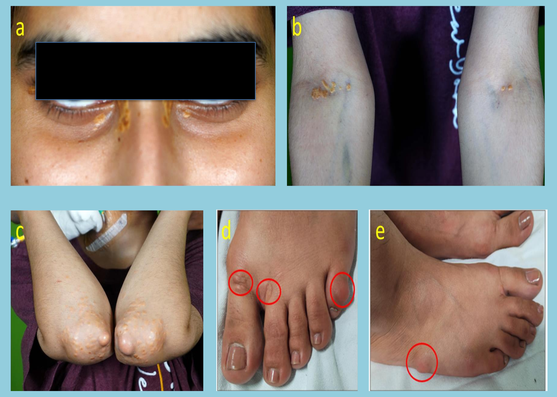

Figure I : Panel of clinical images of the patient showing (a) arcus presenilis, (b,c)- typical tendon xanthomas over flexor and extensor aspects of elbows, (d,e)- atypical sites of eruptive xanthomas

The first LDL apheresis reduced LDL by 84%, but levels returned to baseline after a month. A second procedure, 8 months later, reduced LDL by 67.7%, with effects lasting a month. The patient was prescribed bempedoic acid, rosuvastatin, ezetimibe, and niacin, and had a normal coronary angiogram with minor carotid plaques. She declined further apheresis and liver transplantation, continuing with medication and regular follow-up. However, the response was transient as expected, necessitating frequent use of the procedure. Active research is necessary to create cost-effective cascade filters that are indigenous.

Parameters	2010	2019	2020	2023	2024
Total Cholesterol (mg/dl)	531	914	860	757	780
LDL (mg/dl)	392	894	656	686	656
HDL (mg/dl)	49	26	47	23	20
Triglyceride (mg/dl)	230	179	171	124	175
VLDL (mg/dl)	90	35.8	34.2	38	45

Supplementary Table 1: Changes in LDL and other parameters of the lipid profile over time

DISCUSSION AND CONCLUSIONS

The development of aortic stenosis in HoFH is hypothesized to be due to the effects of persistently elevated LDL-C on the aortic valve.
Statins, while lowering atherosclerosis, may also promote calcification and progression of aortic stenosis in HoFH.
Aggressive lipid-lowering therapies, including LDL apheresis, are crucial in HoFH, but their efficacy is limited once aortic stenosis has developed.
Newer therapies like PCSK9 inhibitors, lomitapide, and evinacumab offer additional options for managing HoFH, but their availability and long-term outcomes are still being evaluated
Homozygous familial hypercholesterolemia is a challenging condition that requires multimodal therapy, including LDL apheresis.
Clinicians should be vigilant for the development of premature valvular dysfunction, in addition to accelerated atherosclerosis, in these patients.

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