Case Report

Access this article online
Quick Response Code:

Website: www.ajts.org
DOI: 10.4103/ajts.AJTS_76_20

# Just not cosmesis! Role of low-density lipoprotein apheresis in familial hypercholesterolemia: Experience at a newly developed tertiary care institution in Northern India

**Daljit Kaur, Gita Negi, Rohit Walia[1], Sheetal Malhotra[2], Riti Bhatia[3], Sushant K. Meinia, Saikat Mandal, Ashish Jain**

**Abstract:**

Familial hypercholesterolemia (FH) is characterized by an increase in plasma low-density lipoprotein-cholesterol (LDL-C) levels. It presents with tendon/skin xanthomas and premature atherosclerotic cardiovascular disease. The most available treatment options for FH are lipid-lowering medications such as statins, lifestyle modification, and LDL apheresis. As per American Society for Apheresis guidelines 2019, the treatment of FH using LDL apheresis falls under Category I. Here, we are reporting an interesting case of a young patient who presented with chief complaints of progressively increasing yellowish lesions around eyes, neck, hands, and legs. She was thoroughly investigated and was diagnosed provisionally as a case of Type 2 FH. Her total serum cholesterol and LDL-C were 717.2 mg/dl and 690.6 mg/dl, respectively, at presentation. One cycle of LDL apheresis was planned for her. We found immediate post-procedural reduction of 55.8% and 55.3% for total serum and LDL cholesterol levels respectively while 70.58% and 77.41% reduction in the levels from the day of presentation to the hospital.

**Keywords:**

Cardiovascular disease, familial hypercholesterolemia, low-density lipoprotein cholesterol, lipoprotein apheresis, xanthomas

*Departments of Transfusion Medicine, [1]Cardiology and [3]Dermatology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, [2]Department of Transfusion Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India*

**Address for correspondence:**
Dr. Daljit Kaur, Department of Transfusion Medicine, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India.
E-mail: doc.daljit@gmail.com

Submitted: 01-06-2020
Revised: 13-12-2020
Accepted: 17-01-2021
Published: 12-06-2021

## Introduction

Familial hypercholesterolemia (FH) occurs due to the mutations in various genes encoding low-density lipoprotein (LDL) receptor (LDLR), apolipoprotein B, proprotein convertase subtilisin-kexin type 9 (PCSK9), or LDLR adaptor protein.[1] The gene dosage can be in the form of homozygous FH (HoFH), heterozygous FH (HeFH), or compound heterozygous (c-HetFH).[1] It is characterized by an increase in plasma LDL-cholesterol (LDL-C) levels in the liver and impairment of LDL-C clearance.[2] If it is not treated timely, patients with HetFH (LDL-C typically >190 mg/dl) develop coronary heart disease (CHD) before the age of 55, while homozygotes (LDL-C typically >500 mg/dl) develop CHD early in life with an average mortality at 18 years.[3] The treatment modalities for FH are multimodal lipid-lowering treatment (LLT) consisting of lifestyle modification, dietary restrictions, statin therapy, PCSK-9 inhibitors, and low-density lipoprotein (LDL) apheresis. The LLT reduces the cardiovascular risk associated with the ongoing accumulation of cholesterol load.

The development of LDL apheresis has led to selective removal of lipoprotein particles



**How to cite this article:** Kaur D, Negi G, Walia R, Malhotra S, Bhatia R, Meinia SK, *et al*. Just not cosmesis! Role of low-density lipoprotein apheresis in familial hypercholesterolemia: Experience at a newly developed tertiary care institution in Northern India. Asian J Transfus Sci 2021;15:104-8.

from the blood while returning the remaining components avoiding loss of beneficial plasma components and eliminating the need of substitution of the same. We are hereby reporting a case of a young female patient who presented to the outpatient department for cosmesis but was hospitalized for further clinical evaluation and management of primary disease.

## Case Report

A 21-year-old female presented to the department of dermatology with chief complaints of gradually progressive yellowish lesions which started around 14–15 years back, first started around eyes and then progressed to neck, hands, arms and legs. The family history revealed the presence of similar symptoms in her elder brother (died 6 years back because of sudden myocardial infarction) and maternal uncle's son. On clinical examination, multiple cutaneous lesions were present including planar xanthomas, tuberous xanthomas, xanthelasma, and corneal arcus [Figure 1]. She was first provisionally diagnosed with hypercholesterolemia at the age of 15 years and was put on lipid-lowering drug statins (5 mg daily) for 1 year and later the dose was escalated to 40 mg daily. At our hospital, she was admitted for radiofrequency ablation and biopsy of the cutaneous lesion in the cubital fossa under department of dermatology. She was further referred for cardiology consultation and her blood investigations were ordered. All her laboratory parameters including complete blood count, serum electrolytes, renal function tests, blood glucose, and liver function tests were normal except lipid profile. Her total serum cholesterol and LDL-C were 717.2 mg/dl and 690.6 mg/dl, respectively. Her treadmill test was positive for inducible myocardial ischemia, and the computed tomography angiogram revealed triple-vessel disease with 100% occlusion of the right coronary artery.

Immediately, treatment was started with 80 mg atorvastatin along with other drugs such as ecosprin, clopidogrel, metoprolol, and nitroglycerin. The department of transfusion medicine was contacted for LDL apheresis in view of coronary involvement and high serum cholesterol levels.

A cascade filtration (CF) plasmapheresis was performed using plasma fractionator (Evaflux 5A20, Kawasumi Laboratories Inc.) with cell separator (COBE Spectra, Terumo Penpol) to withdraw plasma [Figures 2 and 3]. Glicher's rule of five was used for calculation of total blood volume (TBV), and total plasma volume (TPV) was calculated as TBV × (1–hematocrit).[4] As the patient weighed 37 kg, her TBV and TPV were 2405 ml and 1527 ml, respectively. The right femoral vein was used as venous access for procedure using double-lumen femoral catheter. The inlet blood flow rate was kept between 35 and 37.7 ml/min during the procedure. Acid citrate dextrose-A was used as an anticoagulant at a ratio of 1:14, and no replacement fluid was used during the procedure as her own plasma was being returned

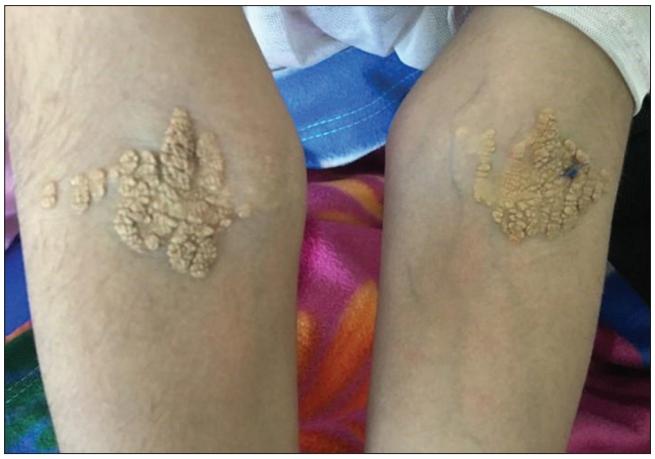

**Figure 1:** Skin xanthomas over the cubital area

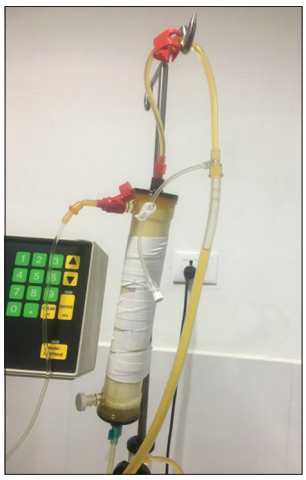

**Figure 2:** Plasma fractionator in use during procedure


**Figure 3:** Ongoing low-density lipoprotein apheresis for our patient

after getting treated through the fractionator column. The procedure was uneventful till the processing of 1.2 plasma volume (1882 ml), when the patient's blood pressure dropped to 70/50 mmHg. The procedure was then halted, normal saline bolus was given, and the procedure was ended with rinseback and the patient was shifted to ward in stable condition. The postprocedural total cholesterol and LDL-C levels were 211 mg/dl and 156 mg/dl, respectively [Figure 4]. Because of financial constraints, the patient could not return for further procedures and enrolled in a free cardiac drug trial. The lipid profile post 12 weeks of drug trial therapy showed raised total serum cholesterol and LDL-C (553 mg/dl and 500 mg/dl, respectively).

## Discussion

LDL apheresis is a therapeutic approach to prevent development of cardiovascular events particularly in those patients who are at an extremely high risk. Various selective and semi-selective extracorporeal methods have been devised for extracorporeal elimination of LDL-C, namely direct adsorption of lipoproteins, Liposorber D (LDL hemoperfusion), heparin-induced LDL precipitation, and CF. Each technology has its own advantages and disadvantages as regards selectivity and cost.[5] CF is a filter-based apheresis technique using different pore sizes that removes pathogenic substances from separated plasma based on their size mainly determined by molecular weight and three-dimensional configuration (e.g., autoantibodies, immune complexes, and lipoproteins).[6] During CF procedure, plasma is separated from blood cells using a centrifugal separation and then perfused through a hollow fiber plasma filter with a surface area of 2.0 m,[2] selectively retaining smaller plasma components such as HDL and albumin but discarding large-molecular-weight atherogenic components such as LDL and Lipoprotein A. Usually, all the different LDL apheresis methods effectively reduce both total and LDL-C levels by >60% and are well tolerated.

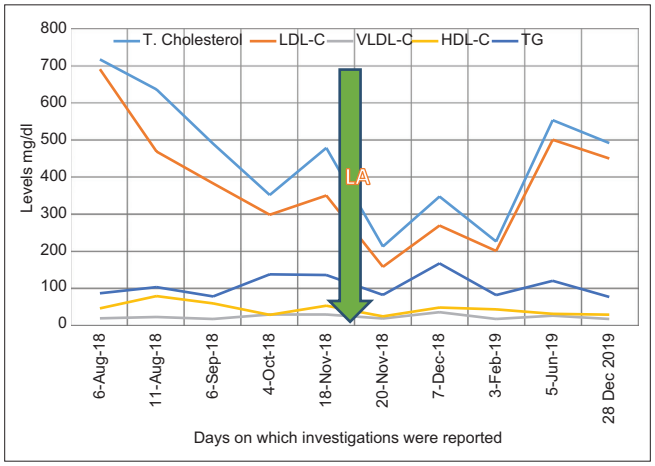


**Figure 4:** Serial laboratory investigations of the patient after presentation to our hospital

The spectrum of LDL apheresis indications as a treatment modality as per American Society for Apheresis (ASFA) guidelines[7] is tabulated in Table 1. HoFH represents a strong indication to start LDL apheresis therapy.[7] Another recognized indication is a severe hypercholesterolemia, which can itself induce cardiovascular events often in association with other risk factors. Our patient, who had severe hypercholesterolemia and clinical features suggestive of HoFH based on her clinical presentation, falls under Category I indication for LDL apheresis as per ASFA guidelines.[7] Higher cost and nonavailability of selective methods made us choose semi-selective CF at our place.

For HoFH patients, LDL apheresis should be initiated at the youngest possible age as coronary stenosis and occlusion are already present in childhood. A multicenter randomized control trial demonstrated that the incidence of coronary artery disease in HeFH patients, who were undergoing LDL apheresis, was lower than those

**Table 1: Current indications of lipoprotein apheresis as per American Society for Apheresis 2019 recommendations[7]**

| Disease | Indication | Category* | Grade of recommendation |
|---|---|---|---|
| Familial hypercholesterolemia | Homozygotes | I | 1A |
| | Heterozygotes | II | 1A |
| FSGS | Recurrent in kidney transplant/ steroid resistant in native kidney | II | 2C |
| Lipoprotein (a) hyperlipoproteinemia | Progressive ASCVD | II | 1B |
| Peripheral vascular diseases | - | II | 1B |
| Refsum's disease (phytanic acid storage disease) | - | II | 2C |
| Hypertriglyceridemic pancreatitis | Severe | III | 1C |
| | Prevention of relapse | III | 2C |
| Sudden sensorineural hearing loss | - | III | 2A |

*I-Accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment. *II-Accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment. *III-Optimum role of apheresis therapy is not established. Decision-making should be individualized. FSGS=Focal segmental glomerulosclerosis, ASCVD=Atherosclerotic cardiovascular disease

receiving only medication therapy.[8] LDL apheresis may be started in patients with raised LDL-C concentrations with effective and tolerated drug therapy and not yet suffered from cardiovascular events.[9] Such patients usually have a family history of cardiovascular diseases and show early atherosclerotic plaques similar to our case, who had family history of cardiovascular disease associated with mortality.

The Japanese Atherosclerosis Society recommended a target LDL-C level in HoFH/HeFH patients of below 100 mg/dl or a reduction of ≥50% in patients targeting primary prevention and of 70 mg/dl in patients for secondary prevention.[10] Immediately post LDL apheresis procedure, our patient's total and LDL- cholesterol levels were reduced by 55.8% and 55.3% respectively. Kardaş *et al*.[11] reported a mean acute reduction of 57.9% and 70.8% in total and LDL-C levels, respectively, while Coker *et al*.[12] witnessed a 63% reduction in LDL-C levels. These studies showed that with ongoing LDL apheresis procedures, there is improvement of myocardial and peripheral blood flow, endothelial function, stabilization and regression of coronary stenosis, widening of coronary artery diameter, and significant reductions in major adverse coronary events.[11,12]

It is reported that reduction of about 50%–60% of the original LDL levels can be achieved with weekly or biweekly treatment.[13] FDA recommends achieving an inter-apheresis LDL-C level ≤120 mg/dl.[14] LDL concentration rebounds after each apheresis session but does not return to the original level and balances out after a few sessions. The postapheresis rebound increment can be slowed down by lipid-lowering drugs, and by lowering the cholesterol from 400 mg/dl to 200 mg/dl, treatment can enhance a patient's life expectancy.[5] Due to financial constraints, our patient was not able to continue regular apheresis therapy. Thereafter, the routine lipid profile of our patient remained high (total serum cholesterol and LDL-C of 553 mg/dl and 500 mg/dl, respectively) and warrants the requirement of regular LDL apheresis.

## Conclusion

LDL apheresis procedures on regular intervals along with diet restriction, and lipid-lowering drugs like statins, prevent early morbidity and mortality in FH patients. Cost–benefit analysis has a strong bearing on how rigorously this therapy can be implemented. The actual practice of LDL apheresis varies in different countries based on awareness/availability and cost constraints related to LDL apheresis therapy. In a resource-constrained country, it still remains a very big challenge to provide a balanced management strategy for the affected patients.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## References

1. Gokay S, Kendirci M, Kaynar L, Solmaz M, Cetin A, Kardas F, *et al*. Long-term efficacy of lipoprotein apheresis in the management of familial hypercholesterolaemia: Application of two different apheresis techniques in childhood. Transfus Apher Sci 2016;54:282-8.
2. McGowan MP. Emerging low-density lipoprotein (LDL) therapies: Management of severely elevated LDL cholesterol--the role of LDL-apheresis. J Clin Lipidol 2013;7:S21-6.
3. Thompson GR, Blom DJ, Marais AD, Seed M, Pilcher GJ, Raal FJ. Survival in homozygous familial hypercholesterolaemia is determined by the on-treatment level of serum cholesterol. Eur Heart J 2018;39:1162-8.
4. Neyrinck MM, Vrielink H; Joint Task Force for Education and Certification. Calculations in apheresis. J Clin Apher 2015;30:38-42.
5. Bambauer R, Bambauer C, Lehmann B, Latza R, Schiel R. LDL-apheresis: technical and clinical aspects. Sci World J. 2012:314283.
6. Kroon AA, van Asten WN, Stalenhoef AF. Effect of apheresis of low-density lipoprotein on peripheral vascular disease in hypercholesterolemic patients with coronary artery disease. Ann Intern Med 1996;125:945-54.
7. Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, *et al*. Guidelines on the use of therapeutic apheresis in clinical practice–evidence-based approach from the writing committee of the American Society for Apheresis: The eighth special issue. J Clin Apheresis 2019;34:171-354.
8. Mabuchi H, Koizumi J, Shimizu M, Kajinami K, Miyamoto S, Ueda K, *et al*. Long-term efficacy of low-density lipoprotein apheresis on coronary heart disease in familial hypercholesterolemia. Hokuriku-FH-LDL-Apheresis Study Group. Am J Cardiol 1998;82:1489-95.
9. Julius U. Current Role of Lipoprotein Apheresis in the Treatment of High-Risk Patients. J Cardiovasc Dev Dis. 2018;5:27.
10. Harada-Shiba M, Arai H, Ishigaki Y, Ishibashi S, Okamura T, Ogura M, *et al*. Guidelines for diagnosis and treatment of familial hypercholesterolemia 2017. J Atheroscler Thromb 2018;25:751-70.
11. Kardaş F, Cetin A, Solmaz M, Büyükoğlan R, Kaynar L, Kendirci M, *et al*. Successful treatment of homozygous familial hypercholesterolemia using cascade filtration plasmapheresis.

Turk J Haematol 2012;29:334-41.

12. Coker M, Ucar SK, Simsek DG, Darcan S, Bak M, Can S. Low density lipoprotein apheresis in pediatric patients with homozygous familial hypercholesterolemia. Ther Apher Dial 2009;13:121-8.
13. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, *et al*. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J 2016;37:2999-3058.
14. US Food and Drug Administration-[Internet]. [An official website of the United States Government]. Available from: Available from: https://www.fda.gov/home.