

## Long term follow-up in a patient with homozygous familial hypercholesterolemia: LDL-apheresis and problems experienced in treatment

Homozigot ailevi hiperkolesterolemi olgusunda uzun dönem izlem: LDL aferezi ve tedavide yaşanan sorunlar

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### Abstract

Familial Hypercholesterolemia (FH) is a genetic disease characterized by extremely high levels of cholesterol leading to cholesterol deposition in skin and tissues and premature atherosclerosis due to defective LDL-receptors. In homozygous individuals (HoFH) cardiovascular events could develop from childhood on. HoFH case reports from our country generally describe the success of the treatments of LDL apheresis or cardiovascular surgery in these young patients. However, there is no information about the long term prognosis of these individuals. This article presents a patient with a long term treatment ( $\geq 7$  years) of LDL apheresis, who had died at the age of 25 because of severe cardiac failure. Even though he had consulted primary care physicians many times with specific physical signs of FH (arcus cornea, xanthomas in the skin) at a very early age and a history of cardiovascular events in first-degree relatives, he could not receive HoFH diagnosis. Due to a delayed diagnosis of HoFH, despite long-term apheresis, atherosclerotic process has progressed. In this case report, the severe problems encountered during the long term management of this HoFH patient are described. At the same time, current treatment approaches for HoFH recommended by the related guidelines are reviewed.

**Keywords:** Familial Hypercholesterolemia, lipoprotein apheresis, LDL-cholesterol, xanthoma.

### Öz

*Ailevi hiperkolesterolemi (AH), LDL reseptörlerinin defektif olması sonucu gelişen aşırı yüksek kolesterol düzeyleri, deri ve dokularda kolesterol birikimi ve erken aterosklerozla karakterize genetik bir hastalıktır. Homozigot olgularda (HoAH) çocukluk döneminden itibaren kardiyovasküler olaylar gelişebilmektedir. Ülkemizden bildirilen HoAH olguları sıklıkla aferez veya kardiyovasküler cerrahinin bu genç hastalarda başarısını aktarmaktadır. Ancak, uzun dönem prognoz hakkında bir bilgi yoktur. Bu makalede uzun süreli (>7 yıl) afereze giren ve ciddi kalp yetersizliği ile 25 yaşında iken ölen bir olgu paylaşılmıştır. Olgu, çok erken yaşta AH'nin tüm tipik bulguları (arkus kornea, deride yaygın kolesterol birikimleri) ve birinci derece akrabalarında erken KV olay hikayesi ile birinci basamak hekimlerine defalarca başvurmasına rağmen tanı alamamıştır. Geç tanı sonucunda uzun yıllar devam eden düzenli afereze rağmen aterosklerotik süreç ilerlemiştir. Bu olgu sunumunda uzun süreli izlemde HoAH hastanın tedavisinde yaşanan ciddi sorunlar aktarılmıştır. Aynı zamanda HoAH için kılavuzların önerdiği güncel tedavi yaklaşımı gözden geçirilmiştir.*

**Anahtar Sözcükler:** Ailevi hiperkolesterolemi, lipoprotein aferezi, LDL-kolesterol, ksantom.

### Introduction

Familial Hypercholesterolemia (FH) is characterized by cholesterol deposition and premature atherosclerosis due to genetically defective low density lipoprotein (LDL) receptors (1,2).

Patients with homozygous FH (HoFH) have extremely high serum cholesterol levels (>500 mg/dL). Severe ostial coronary artery disease (CAD) and aortic stenosis (AS) develop starting from early childhood due to life-long exposure to elevated cholesterol (1,2). Antilipid medications remain ineffective in HoFH due to absent or defective LDL-receptors. HoFH patients should undergo LDL-apheresis or liver transplantation at early ages for survival. Herein we present an adult HoFH patient, who had been regularly undergoing LDL-apheresis since

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Received: 19.04.2016

Accepted: 05.06.2016

childhood in our Lipid Clinic. Parents of the patient provided informed consent for the use of his medical history belonging to his childhood period in the article.

### Case Report

Herein we present a typical case of HoFH associated with proximal coronary artery and aortic involvement. He had visible lipid depositions since he was 4 years old (Figure-1).

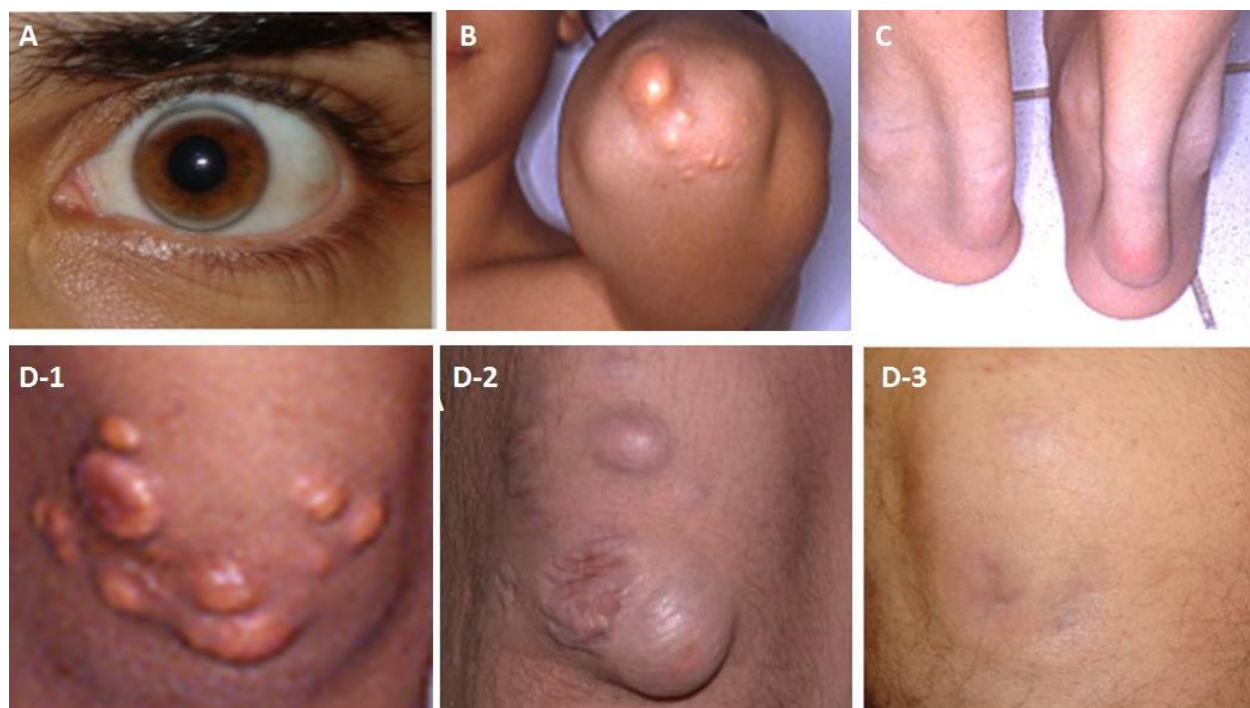
His family history was remarkable for hypercholesterolemia and CAD with no consanguineous marriages. Despite the definite clinical picture for HoFH, he had been treated empirically with antibiotics for xanthomas.

At the age of 9 years, a pediatric endocrinologist had noticed extremely high cholesterol levels and had informed his family about HoFH for the first time. He was compound heterozygous with two different LDL-receptor defects (allele-1:C292, exon-6 and allele 2:2400delCTTC, exon-17). He had reported to have severe AS (maximal-gradient 82 mmHg) with typical proximal coronary involvement (50% stenosis in left main coronary artery proceeding to left coronary artery and 50-60% in mid-circumflex artery). Though aortic replacement and coronary bypass grafting was recommended, his family did not give consent for surgery. At the age of 13, LDL-apheresis treatment was

initiated and continued biweekly for 5 years in our Pediatric Metabolism Department. However, at the age of 18 years, he was lost to follow-up.

At the age of 21 years, he was admitted to our cardiology department with the complaint of angina pectoris. AS (maximal /mean gradients of 100/66 mmHg) had progressed during the non-treatment period, while the left ventricular ejection fraction had decreased (40%). There was significant calcification both in the aortic root and valve. He did not give consent for surgery. He underwent LDL-apheresis biweekly for 3 years regularly and angina vanished. As he was full-time employed, arranging apheresis timing was difficult and affected his compliance. Therefore, he refused apheresis and one year later he died at the age of 25 years due to progressive heart failure. He was hospitalized 18 times totally during his last 4 years (3 years on apheresis plus the last non-apheresis 1 year) due to worsening of the heart failure (10 times), severe anemia - blood transfusion (3 times), pulmonary embolism (once), pneumonia (twice) and bacteremia (twice; catheter infection once and endocarditis). Type III aortic dissection was also detected.

Written informed consent was obtained from the patient for publishing the individual medical records.



**Figure-1.** Examples for the patient's cholesterol depositions **A.** Arcus lipemia in the cornea (at 23 years of age, while on a regular apheresis treatment for 3 years), **B.** Cholesterol deposition on the extensor surface of the elbow (at 13 year of age), **C.** Thickening of the Achilles tendon due to cholesterol deposition (at 13 years of age) **D.** Deposition in the skin on the extensor surface of the knee-joint D-1. Before apheresis at 13 years of age, D-2. After a 3-year discontinuation of apheresis at 21 years of age, D-3. Cholesterol deposition on the extensor surface of the knee-joint disappearing after 3 years of regular apheresis.

## Discussion

Despite the presence of skin findings and strong family history of our patient, the subject had not been considered for the diagnosis of FH in his early presentations. Late diagnosis has led to the progression of the atherosclerosis and has delayed the commencement of apheresis. For HoFH, LDL-apheresis is a lifesaving treatment decreasing cardiovascular events and enables the regression of xanthomas (3,4). The patient underwent regular LDL-apheresis for 5 years. Lipid levels were reduced to target levels, however AS has progressed. In fact, guidelines recommend starting LDL-apheresis in early childhood (<6-7 of age) in order to prevent AS (5). Apheresis, which was started at around the age of 10, was not able to prevent the progression of AS, even if it was effective in lowering LDL. Moreover, the atherosclerotic process might progress in 25% of the patients despite regular and effective lipid apheresis (6). This could be explained by the non-sustained lipid decrease ensured by apheresis. LDL-cholesterol levels achieved at the end of each apheresis session rapidly increase to its former level in

the following days. Moreover, apheresis is an invasive procedure with drawbacks and is also a chronic and time requiring therapy that leads to decreased compliance. Thus, more easily applicable new treatment options (7) are needed for achieving more effective lipid decrease with much more continuity and consistency.

HoFH cases in the literature are generally presented for the short term success of treatments with lipid lowering agents and/or apheresis. The longest survived patients are reported to have passed the age of 50 (8). However, these long surviving patients in general have considerably lower pre-treatment cholesterol levels denoting a less severe genetic defect in the cholesterol pathways. Our patient was a severe form of HoFH associated with a cholesterol level of 1002 mg/dl at the time of diagnosis.

Patients with HoFH are at severe risk for premature cardiovascular events and need to be treated very early (9). Therefore, early diagnosis is the key point in the management of HoFH in order to prevent lifetime exposure to high cholesterol levels leading to premature atherosclerosis including AS.

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