

## A Case of Refractory Type III Hyperlipoproteinemia Successfully Treated with Plasmapheresis

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### SUMMARY

*A 42-year-old male was hospitalized in Department of Endocrinology for evaluation of persistent hypertriglyceridemia and hypercholesterolemia. He was normal on physical examination except having multiple xanthomas in elbow, knee and ankle. ApoE genotyping was performed by PCR and apoE phenotype was found to be E2/E2. Firstly, he was treated with atorvastatin (40mg/day) and niacin (1500mg/day) but it was found that the patient did not respond after three months of the treatment. Then he was treated with plasmapheresis twice a week. After three weeks of plasmapheresis treatment triglyceride and cholesterol levels were markedly decreased.*

*Plasmapheresis can be highly effective in removing the lipoprotein-remnant particles, leading to generalized improvement in the lipoprotein profile in severe type III hyperlipidemia, which do not respond to conventional therapies as in our case.*

*Key Words: Plasmapheresis, Type III Hyperlipidemia, E2/E2*

## Plazmaferez ile Başarılı Bir Şekilde Tedavi Edilen, Ciddi Tip III Hiperlipoproteinemili Bir Olgu

### ÖZET

*Kırkiki yaşındaki bir erkek hasta var olan hipertrigliseritemi ve hiperkolesterolemisini araştırmak üzere endokrinoloji kliniğine yatırıldı. Hastanın fizik muayenesi dirsek, diz ve ayak bileğinde var olan ksantomlar dışında normaldi. PCR ile değerlendirilen Apo E genotipi E2/E2 olarak belirlendi. Hastanın tedavisi için ilk önce atorvastatin 40 mg/gün ve nikotinik asit 1500mg/gün dozunda başlandı, ancak üç ayın sonunda bu tedaviye cevap alınamadığı gözlemlendi. Sonra hastaya haftada iki kez plazmaferez uygulandı, üç hafta sonrasında total kolesterol ve trigliserit düzeyleri anlamlı olarak azaldığı görüldü.*

*Sonuç olarak konvansiyonel tedavilere cevap vermeyen ciddi tip III hiperlipidemi olgularında plazmaferez, lipoproteinlerin ortamdaki uzaklaştırılmasını sağlar ve lipid profilinde genel bir iyileşme oluşturur.*

*Anahtar Kelimeler : Plazmaferez, Tip III Hiperlipidemi, E2/E2*

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## INTRODUCTION

Type III hyperlipoproteinemia (HLP), or dysbetalipoproteinemia is a genetic disorder of lipid metabolism that predisposes affected subjects to the premature development of atherosclerosis (1). Type III HLP should be suspected in an individual with: 1) mixed hyperlipidaemia (serum total cholesterol  $>8\text{mmol/l}$  and serum triglyceride  $>5\text{ mmol/l}$ ) 2) palmar striae and/or tuberoeruptive xanthomata, remnant (floating beta) lipoprotein, or defective apo E isoforms (2). Homozygosity for apolipoprotein E2, the presence of an abnormally cholesterol-rich very low density lipoprotein fraction (beta-VLDL) and an elevated ratio of very low density lipoprotein cholesterol to plasma triglycerides ( $> 0.3$ ; normal ratio about 0.2) were the basis for the diagnosis (3). The prevalence of type III HLP was 1 to 5 per 5000 in white populations (4, 5). A restricted diet intake combined with lipid-lowering drugs such as, statins, clinofibrate, and bezafibrate, was not very effective in lowering serum triglyceride and cholesterol levels within physiological ranges. Plasmapheresis could be choice of treatment especially in the severe forms of Type III HLP (6). Herein we report a case of refractory type III HLP successfully treated with plasmapheresis.

## CASE

A 42-year-old Caucasian male was hospitalized in Dicle University School of Medicine, Department of Endocrinology and Metabolism for evaluation of persistent hypertriglyceridemia and hypercholesterolemia. He was not an active smoker and seemed normal on physical examination except having multiple xanthomas in elbow, knee and ankle (figure-1). The blood pressure was 140/100 mmHg, the pulse rate was normal, and peripheral pulses were palpable.



**Figure-1 a.** multiple xanthomas of knee



**Figure-1 b.** multiple xanthomas of the ankle

**Biochemistry:** Fasting glucose: 91 mg/ml (70-115mg/dl), urea:35mg/dl (10-45mg/dl), creatinine:0.9mg/dl (0.5-1.4 mg/ml), Na:138 mmol/L (136-145mmol/L), K:4.6mmol/L(3.5-5.1mmol/l), Ca:9.7 mg/dl (8.4-10.2mg/dl), AST:18 U/L (10-40U/L), ALT:31 U/L (10-35 U/L), albumin:4.1/dl (3.5-5g/dl), triglyceride:16.3mmol/l (0.57-2.26mmol/l) total-cholesterol:18.2 mmol/l (2.9-5.18), HDL-cholesterol:0.75mmol/L(0.73-1.63 nmol/L), LDL-cholesterol: 8.57mmol/L (1.55-4.14mmol/L), VLDL-cholesterol: 5.51mmol/l(0.11-0.36mmol/L). VLDL-cholesterol/ triglycerides ratio: 0.34

**Hormonal analyzes:** Total T3:1.74 ng/ml(0.84-2.02 ng/ml), total T4 7.65  $\mu\text{g/dl}$  (5.13-14.06 $\mu\text{g/dl}$ ), free T3: 0.210 ng/dl (0.182-0.462ng/dl) free T4:1.28 (0.932-1.71ng/dl), TSH:1.49IU/L(IU/L)



Plasma lipoprotein electrophoresis in agarose gel showed a broad b-band. The VLDL fraction on electrophoresis had b-migrating lipoproteins. DNA was extracted from white blood cells using 'blood PCR' DNA isolation cartridges. ApoE genotyping was performed by polymerase chain reaction and apoE phenotype was found to be E2/E2. An electrocardiogram display sinus rhythm and inferior ischemia. The chest radiography showed no abnormality, and echocardiogram had left ventricular hypertrophy. Coroner angiography revealed right coronary artery (70%) and left coronary artery (60%) stenosis. The patient has five children (3 female and 2 male). All children were healthy with respect to lipid disorders. None of the family members revealed symptoms of coronary and/or peripheral vascular disease. We initiated a trial of plasma exchange therapy in an attempt to reduce the debilitating effects of the patient's excess plasma lipids by physical means. Procedures were performed using continuous flow centrifugation (CS-3000 Plus Blood Cell Separator-Baxter) (with bilateral antecubital venous access. The patient underwent plasmapheresis twice a week. Human Albumin in 5% concentration was used for plasmapheresis instead of plasma. A total of one volume plasma was exchanged in one procedure. The aphaeresis was generally well tolerated. Vasovagal symptoms with vertigo and nausea occurred in the first week of plasmapheresis. Repeated plasmapheresis markedly reduced serum TC and TG (table-1). Plasmapheresis was highly effective in removing the lipoprotein-remnant particles in this patient, leading to generalized improvement in the lipoprotein profile.

**Table.**

	Basal	Plasmapheresis is first week	Plasmapheresis second week	Plasmapheresis is third week
Triglycerides(mmol/l)	16.3	15.9	10.7	7.18
Total cholesterol(mmol/l)	18.2	14.0	6.99	6.71
HDL-cholesterol(mmol/l)	0.75	0.67	0.60	0.62
LDL-cholesterol(mmol/l)	8.57	5.78	3.92	3.06
VLDL-cholesterol(mmol/l)	5.51	3.49	2.03	1.44

## DISCUSSION

Type III hyperlipoproteinaemia presents in early adult life and is often associated with obesity, glucose intolerance and hyperuricaemia. Yellow palmar creases, palmer xanthomas and tuberoeruptive xanthomas may be present. There is an increased risk of coronary artery disease (this condition may be found in approximately 3% of survivors of myocardial infarctions) and peripheral vascular disease. The primary molecular cause of type III HLP is the presence of apoE2, which differs from the most common isoform of apoE (apoE3) by a single amino acid substitution (cysteine for arginine at residue 158) and is associated with recessive inheritance of the disorder (1). The mode of inheritance needs further exploration, since recessive and dominant inheritance has been reported (7). The disorder in our patient is not the result of autosomal dominant type III disease, since there is no family history of lipid disorders. In this manifestation, development of overt hyperlipidemia requires homozygosity for apoE2. However, less than 10% of apoE2 homozygotes develop the hyperlipidemia; despite the invariable presence of  $\beta$ -VLDL, most apoE2/2 subjects are either normolipidemic or even hypocholesterolemic (4, 8). Therefore, additional genetic, hormonal, or environmental factors, such as obesity, hypothyroidism, estrogen status, or diabetes, are required to precipitate the hyperlipidemia. There was no evidence for diabetes mellitus, hypothyroidism, renal dysfunction or liver disease of our patient. Type III HLP is much more common in men and tends to occur earlier in men than in women, who rarely develop the disease until menopause. Clinical features: xanthomata is present in about 50% of patients with type III hyperlipoproteinaemia; characteristically striate palmar xanthomata (may be an orange discoloration of skin creases or may be raised papules in the skin creases of the palms, fingers and flexor surfaces of the wrists) and tuberoeruptive xanthomata (often occur over the elbows and knees). The patient has xanthomata at his elbows knees and ankle. If typical xanthomata is present together with associated high levels of cholesterol and



triglyceride - further laboratory tests are generally not required for the diagnosis. If xanthoma is absent, then hyperlipoproteinaemia with similar levels of cholesterol and triglyceride can occur in type IIb or V hyperlipidaemia.

Currently there are 3 techniques to remove LDL from plasma: LDL immunoadsorption, dextran sulfate chemoabsorption, and heparin-induced extracorporeal LDL precipitation (H.E.L.P.) While lipid apheresis is relatively safe, it may occasionally be associated with significant hypotension and anaphylactoid reactions. Hypotension may be more common with dextran sulfate chemoabsorption in patients who are taking ACE inhibitors. There are no adequate trials comparing various LDL pheresis techniques. While these techniques are predominantly selective for LDL, other substances may be removed as well, including fibrinogen and bradykinin. It is unclear whether there is significance of removal of these factors (9, 10)

Lipoprotein electrophoresis is useful in differentiating type IIB from type III hyperlipidemia if it can show separate pre- $\beta$  VLDL and  $\beta$  LDL bands. Our patient showed both separate pre- $\beta$  VLDL band in lipoprotein electrophoresis and xanthoma. Firstly, for the treatment of patient, atorvastatin 40mg/day and niacin 1500mg/day were started but triglyceride and cholesterol levels did not decrease after three months (decreasing of triglycerides level was 100 mg/dl). Plasmapheresis was used to removing the lipoprotein-remnant particles in this patient. This technique was very successful to improve the lipoprotein profile in our patient. Plasmapheresis can be highly effective in removing the lipoprotein-remnant particles, leading to generalized improvement in the lipoprotein profile in severe type III hyperlipidemia, which do not respond conventional therapies as in our case.

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