

Hypertriglyceridemia: Is there a role for prophylactic apheresis? A case report

Hipertrigliceridemia: há um papel para a aferese profilática? Relato de um caso

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ABSTRACT

Severe hypertriglyceridemia has been consistently associated with an increased risk of cardiovascular disease and other complications, namely acute pancreatitis. We report a case of a 64 year-old woman with hypertrophic cardiomyopathy and metabolic syndrome with triglyceride level of 3260 mg/dL. Plasma exchange was performed with simultaneous medical treatment to achieve a rapid and effective lowering of triglycerides in order to prevent clinical complications. After three plasmapheresis sessions a marked reduction in triglyceride and total cholesterol levels was observed. Several cases have shown the importance of plasmapheresis in the treatment of acute pancreatitis. We intend to demonstrate the applicability of this technique as primary prophylaxis in the presence of extremely high serum triglyceridemia levels.

Keywords: cardiovascular diseases; hypertriglyceridemia; plasmapheresis; primary prevention.

RESUMO

A hipertrigliceridemia grave tem sido associada de forma consistente ao aumento do risco cardiovascular e a outras complicações, nomeadamente, pancreatite aguda. Descrevemos um caso de uma mulher de 64 anos, com miocardiopatia hipertrófica e síndrome metabólica com valor sérico de triglicéridos de 3260 mg/dL. Foi efectuada plasmaferese e optimizado o tratamento médico para alcançar uma redução rápida e efectiva dos níveis dos triglicéridos, prevenindo complicações clínicas. Após três sessões de plasmaferese, verificou-se uma redução marcada dos triglicéridos e do colesterol total. Existem alguns casos descritos na literatura demonstrado a importância da plasmaferese no tratamento da pancreatite aguda em contexto de hipertrigliceridemia grave. Os autores pretendem com este caso demonstrar a aplicabilidade desta técnica em contexto de prevenção primária em doentes com níveis de triglicéridos extremamente aumentados.

Palavras-chave: doenças cardiovasculares; hipertrigliceridemia; plasmaferese; prevenção primária.

INTRODUCTION

Hypertriglyceridemia (HTG) results from elevation in the lipoproteins responsible for triglyceride (TG) transport. It is more frequently secondary to high alcohol intake, obesity, unmanaged diabetes or as an adverse effect of medication. Mild-to-moderate HTG is typically a polygenic disease and severe elevation of TG levels can be caused by rare, recessive monogenic disorders.¹

Apart from cardiovascular disease, severe HTG (TG > 885 mg/dL) is consistently associated with an increased risk of

acute pancreatitis, hepatosplenomegaly, eruptive xanthomas and lipemia retinalis. Usual preventive measures for treatment include fat-reduced diet (with avoidance of simple carbohydrates), and lipid-lowering agents, such as medium-chain triglycerides, omega-3-fatty acids, fibrates and nicotinic acid. However, these measures have a slow effect and frequently low efficacy.

Patients with severe HTG require a fast and effective lowering of TG levels in order to prevent/treat an acute pancreatitis episode and prevent cardiovascular complications.²⁻⁴ Current data suggest

that apheresis is an option to treat acute pancreatitis and to prevent relapses when medical treatment fails and should be performed as soon as possible to achieve the best results.^{4,5}

Recently, therapeutic plasma exchange (TPE) has been used in severe HTG for the prevention of complications with good results, in patients not responding to usual medical treatment.^{6,7} However the use of apheresis in primary prevention of HTG complications is limited due to lack of availability and high costs of the technique.

CASE REPORT

A 64 year-old woman with sarcomeric hypertrophic cardiomyopathy (point mutation at exon 11 in the *LMNA* gene), type 2 diabetes, obesity (BMI = 30) and familial combined hyperlipidemia (inconclusive genetic test) was admitted to our cardiovascular department due to worsening cardiac symptoms, with orthopnea and marked limitation in daily activities (heart failure, NYHA class III).

There was no history of alcohol consume or smoking. Coronary angiography performed eight months before revealed normal coronary arteries. She was under treatment for her heart condition (hypertrophic cardiomyopathy with chronic heart failure and preserved ejection fraction) including nebivolol 5 mg bid, amlodipine 5 mg qd, spironolactone 25 mg qd and furosemide 40 mg qd plus rosuvastatin 10 mg qd. Upon admission she presented with xantomas and fulfilled the criteria for the diagnosis of metabolic syndrome - fasting glucose ≥ 100 mg/dL, triglycerides ≥ 150 mg/dL, HDL-C < 50 mg/dL and waist circumference ≥ 88 cm.

Laboratory tests revealed a fasting serum TG level of 3260 mg/dL, total cholesterol of 640 mg/dL, high-density lipoprotein (HDL) of 26 mg/dL, HbA1c of 6,8% and a creatinine value of 1,0 mg/dL. A prior laboratory evaluation, 6-months before, showed a triglyceride plasma value of 1000 mg/dL. At that moment, a low-fat diet and rosuvastatin 10

mg were prescribed and a lipid-consultation was recommended. No aggravating factor for HTG was identified.

Despite the absence of acute pancreatitis, in order to achieve a fast and effective lowering of TG values and prevent complications due to HTG, the Nephrology department was contacted to provide TPE. Centrifugal TPE was performed in three consecutive days (using a 12 Gauge right femoral hemodialysis catheter), with a 1.5 total plasma volume replaced with albumin solution (mean time of 106 min per session), and with use of heparin as anticoagulant. There was a marked reduction in TG levels (and also in total cholesterol levels) (Table 1).

At the same time the treatment with lipid-lowering agents was intensified with addition of bezafibrate 200 mg bid. No complications were reported. The patient was discharged a few days later treated with rosuvastatin at 20 mg qd, bezafibrate at 200 mg bid and ezetimibe at 10 mg qd. Heart failure therapy was also intensified. In her first reevaluation one month after discharge she was asymptomatic and her lipid profile remained significantly improved (Table 1).

DISCUSSION

In recent years, the focus on cardiovascular disease prevention has been LDL cholesterol lowering. Less emphasis has been placed on lowering TG because of its minor role in cardiovascular disease (CVD) and controversial benefits. As early as 1953, high levels of TG were reported among myocardial infarction patients.⁷ Subsequently, studies showed that this combination was not superior after correction for other lipid risk factors (especially HDL cholesterol level).⁸

In addition, many individuals with extremely high TG concentrations did not develop atherosclerosis or CVD. This observation may in part be explained by the fact that with high concentrations of TG (> 4425 mg/dL; > 50 mmol/L) triglyceride-containing lipoproteins are too large to enter into the arterial intima. This does not happen with mild-to-moderate elevations (177-885 mg/dL; 2-10 mmol/L).⁹

TABLE 1 LIPIDIC PROFILE AT THE END OF EACH SESSION OF PLASMAPHERESIS AND AT 1 MONTH FOLLOW-UP

	Initial value	1 st session	2 nd session	3 rd session	1 month follow up
Total cholesterol (mg/dL)	640	402	98	83	150
Triglycerides (mg/dL)	3260	1350	527	369	301
HDL (mg/dL)	36	32	14	16	39
LDL (mg/dL)	TI ^a	TI	TI	219	51

^a Technical impossibility due to high triglycerides level (> 400 mg/dL)

However, new epidemiological and genetic studies pointed out that high concentration of TG is not only a marker of cardiovascular risk, but is also predictive of higher cardiovascular and all-cause mortality.¹⁰ TG have a direct impact in the atherosclerotic process through cholesterol-enrichment lipoprotein particles.

This in turn leads to dysfunctional HDL and more susceptible to oxidative modification LDL, with an increased number of atherogenic particles, all of which influence global cardiovascular risk.¹¹ Additionally, patients with severe HTG had significantly higher concentrations of plasma fibrinogen and clotting factor Xc, leading to a more prothrombotic state.¹²

Therefore, effective measures for TG reduction are necessary. Since the first description of TPE in severe HTG in 1978, several small studies and case reports have been published, most of them focusing on treatment of acute pancreatitis.¹³ This treatment is now approved by the American Society of Apheresis (ASFA) Committee on Clinical Application (category III practice^[a]) for HTG patients in the presence of severe pancreatitis. Acute pancreatitis should be a concern when TG > 500-1000 mg/dL, and is quite probable when TG > 2000 mg/dL.

In order to treat HTG, TPE can be performed by either centrifugal or double membrane filtration. A comparison of these two methods found greater TG removal with centrifugal methods because of the TG tendency to clog the filters' pores. There are no reports concerning a higher risk of system coagulation in these patients (despite the prothrombotic state). Heparin should be the anticoagulant of choice, because of its ability to release LPL, enhancing TG reduction.¹⁴

Usually, one to three sessions are effective in lowering TG levels and to reduce the clinical manifestations of pancreatitis. This treatment should be performed until TG levels are lowered to < 500 mg/dL, followed by an intense nutritional and pharmacologic intervention to achieve a persistent effect. In some cases, it is necessary to maintain regular, long-term TPE sessions (e.g. 1 session every 4 weeks). Patients undergoing chronic TPE to prevent recurring pancreatitis have a lower risk of pancreatitis, resulting in fewer hospitalizations and reduced health costs.^{5,15}

In this case, the patient was previously under a sub-optimal medical treatment for HTG, which

may have contributed to the severe HTG observed. Attending to the risk of acute pancreatitis associated, urgent TG level reduction was deemed necessary, that could only be achieved through TPE, associated with simultaneous intense lifestyle change and pharmacological therapy optimization.

Several complications of plasma exchange are described including infection, allergic reaction and bleeding.¹⁶ Despite these, in the majority of cases reports, this technique isn't associated with adverse effects. TPE is therefore a safe, rapid and highly effective treatment for emergency management of severe HTG.^{4,17} Because of the safety of the technique and the need to prevent serious complications associated with HTG, some authors now recommend apheresis in patients with serum TG level > 1000 mg/dL, regardless of symptoms.⁶

However, some questions remain unanswered, namely if the risk of acute pancreatitis is proportional to the level of TG in severe HTG, and whether the threshold for TPE should be the same for primary and secondary prevention.

Finally, it should be noted that some rare cases of severe hypertriglyceridemia have been described in the context of the *LMNA* gene mutations. Further investigations are needed to link these two findings.^{17,18} To note that mutations in the *LMNA* gene are usually described in association with dilated cardiomyopathy and not with hypertrophic cardiomyopathy, as was the case of our patient.

However, her cardiac phenotype - important left hypertrophy (septal thickness of 21 mm) in the absence of other identifiable cause - and the identification of a unique pathogenic mutation in a sarcomery-related gene (point mutation in exon 11 in *LMNA* gene) (in a panel of 51 genes associated with cardiomyopathies) suggested a causal association between molecular genetic findings and the cardiac phenotype. Also, an enormous variability of cardiac muscular involvement in patients with mutations in Lamin A/C genes are described.¹⁷

In conclusion, TPE is a reasonable option to rapidly and effectively reduce high TG levels, reducing complications and avoiding health costs and hospitalizations both in primary and secondary prevention. However, it remains a treatment modality that is not available in all medical centers. Additional prospective studies, comparing medical with apheresis treatment in order to prevent cardiovascular and other HTG complications are needed.

[a] Category III is defined as "Optimum role of apheresis therapy is not established. Decision making should be individualized."

Conflict of Interest: The authors declare that they have no conflict of interest.

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