ISSN: 2573-9565

Case Report

Journal of Clinical Review & Case Reports

The First Sign of an Impending Disaster? Headache in a Patient with Severe Hypertriglyceridemia - the Need for Preventive Plasmapheresis

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Submitted: 14 July 2018; **Accepted**: 19 July 2018; **Published**: 01 Aug 2018

Abstract

Hypertriglyceridemian has been shown with accumulating evidence to contribute to ischemic stroke through many pathologic processes such as endothelial dysfunction, atherosclerosis and production of prothrombotic state, in addition to hypergoagulability and slugging [1]. Recent evidence suggests that hypertriglyceridemia may correlate with increased risk of cardiovascular disease, especially when associated with decreased HDL- C, increased LDL- C levels, or both [2]. However the debate remains whether Hypertriglyceridemia is an independent risk factor for ischemic stroke.

Case Report: *We present a case of 44 year old male patient with history of hypertriglyceridemia, who presented with severe headache, worsening over the last few days before admission. His triglycerides level was 10308 on admission. The headache was alarming and was considered as a sign of hyper viscosity with subsequent vaso- occlusive disease. He was started on IV insulin drip initially with minimal change in his triglycerides level over a 3- day period. With persistence of headache, the patient was started on plasmapheresis with dramatic resolution of the headache as the triglyceride levels dropped markedly.*

Conclusion: *The use of plasmapheresis should be considered in patients with severe persistent hypertriglyceridemia, especially in patients who have persistent alarming headaches or signs if impending cerebral vaso- occlusive disease. Plasmapheresis should be considered primarily for stroke prevention in this population.*

Introduction

Stroke is a deleterious condition, with direct impact on the patient's well being on many levels, including health, socioeconomic, functional, comprehensive and social functioning. Ischemic stroke is a well established morbid condition, with large efforts placed aiming at its primary prevention, as well as secondary prevention. Multiple independent risk factors have been identified, including hypertension, diabetes, smoking, A-fib, CAD, CHF and dyslipidemia. Low HDl- C and high LDL- C are possible independent risk factors for ischemic stroke [3, 4]. Hypertriglyceridemia is an established risk factor for stroke, where high triglycerides levels were found in the 3 major stroke subtypes as compared to controls [5]. Recent evidence suggests that hypertriglyceridemia may correlate with increased risk of CVD [2]. Hypertriglyceridemia can present with many symptoms, with some considered as alarming for stroke. Patients with DM, HTN and persistently high triglycerides, presenting with severe bilateral unrelenting headache, especially when triglycerides remain high despite conventional therapy, should be considered at high risk for impending stroke, and more aggressive measures should be considered in the acute management hypertriglyceridemia.

Case Report

We present a case of a 44 year old male pt with past medical history of HTN, familial HLD, type 2 DM, COPD, depression and chronic alcoholic pancreatitis presenting to the hospital with severe pounding bilateral frontal headache that has been worsening over the last few days before admission. His headaches were associated with nausea and poor appetite. The patient denied any vomiting, visual disturbances, focal weakness or seizures. Physical examination was unremarkable, except for black discoloration of the tip of his left fourth toe. CT head was negative for acute intracranial process. His admission labs showed serum Na of 114 and blood sugar of 358. Work up for hyponatremia showed normal plasma osmolarity and normal urine osmoarity. Further workup showed that the pt TG level was 10308. Corrected Na level was 140.

The patient was on 4 lipid lowering medications including Atorvastatin 80 mg daily, Gemfibrizole 600 mg twice daily, Niacin 500 mg daily and Fish oil 1000 mg twice daily. The patient was not compliant with his dyslipidemia or diabetes medications. Upon admission, the patient was restarted on his lipid lowering medications. The patient's complaint of persistent headache was alarming, especially in the presence of necrotic left foot toe. The patient was placed in the critical care unit, and was started on Insulin drip and dextrose via continuous infusion. His TG level was dropping about 1000 mg/dl, reaching 9390, 7836 and 6929 over 3 days. However the patient continued to complain of headache with mild improvement.

The decision was made to start the patient on plasmapheresis for fear of impending stroke. The strategy was to perform 3 sessions every other day, with albumin for fluid replacement with 1:1 volume, citrate for anticoagulation and Calcium gluconate, with continuous monitoring of the patient symptoms and triglyceride levels.

With plasmapheresis started, plasma was grossly lipemic, and milky in color. Triglyceride dropped to 1747 (75% drop from the day before and 83% from initial TG level) after 1 session. IV insulin was discontinued and the patient was started on Lantus 50 daily, Novalog 15 unit's tid with jeals in addition to sliding scale.

On the 3rd day after initial plasmapheresis, triglyceride level increased to 2157. Another plasmapheresis session was done, with TG level of 62 afterwards. TG rose again to 1340 after that and the patient received a 3rd session of plasmapheresis. The patient reported marked improvement of his headaches with minimal residual headaches after the 3rd session.

The patient was discharged after complete resolution of his symptoms and control of TG level. On discharge, TG level was 794. His Insulin was adjusted to 65 units of Lantus, 20 units of Novalog three times daily and sliding scale. He was recommended to follow in the outpatient clinic for assessment for the need of a 4th session of plasmapheresis after 1 month, if his TG starts to rise again.

Discussion

Hypertriglyceridemia is a disorder of TG metabolism, with 33% of adults having borderline elevation of TG (150- 199 mg/dl), the percentage becomes 1.7% for TG > 500, and 0.4 % for levels above 1000 mg/dl [6]. Severe hypertriglyceridemia refers to levels above 886 mg/dl [7]. Some authors define severe hypertriglyceridemia with TG levels above 1000 mg/dl, and very severe above 2000 mg/dl [8]. Usually patients with hypertriglyceridemia have controlled TG levels with medications. However patients with uncontrolled hypertriglyceridemia usually have concomitant uncontrolled diseases such as DM. these patients often have associated medication/ diet non- compliance, which are the major contributors to having high uncontrolled TG levels [9,10].

Recent evidence suggests that hypertriglyceridemia may correlate with increased incidence of cardiovascular disease, especially in the setting of increased LDL- C, decreased HDL- C or both [2]. Suggested mechanisms include endothelial dysfunction, oxidative stress due to ROS and other free radicals from TG metabolism and impairment of endothelium- dependent vasodilation [11]. In 1 observational study, chronic hypertriglyceridemia was independently associated with endothelial dysfunction in patients with normal LDL- C [12]. Another mechanism was accelerated atherosclerosis through association with CRP. While the increased risk of CAD with elevated CRP doesn't appear to be associated with elevated LDL-C, LDL- TG (a type of LDL protein) does appear to be associated with elevated CRP, and increased risk of CAD. Some studies found that LDL- TG was a stronger predictor of CAD than LDL- C [13-16].

One observational study reported increased association between carotid wall thickness and postprandial hypertriglyceridemia, where investigators found that persons with higher postprandial TG levels had the greatest degree of carotid intima- media thickness on u/s [17].

Another mechanism by which TG are suggested to contribute to cerebrovascular disease is through its effect on thrombosis, by thrombogenic alteration of the coagulation system and elevating plasma viscosity [18]. Patients with severe hypertriglyceridemia (mean TG 504.4 mg/dl) had higher levels of clotting factor X, compared to people with normal lipid levles, and elevated fibrinogen level has been found to be a powerful independent predictor of vascular events, and it was associated with progression of carotid artery disease [19, 20]. Hyperviscosity associated with severe hypertriglyceridemia can lead to tissue ischemia due to impaired microcirculation, damage to endothelium and increase thrombogenic tendency, where lowering of TG levels lead to decreasing of viscosity without changing fibrinogen levels [21-23].

Elevated TG levels were documented in all 3 stroke subtypes, and therefore don't seem to be significantly related to one stroke subtype [5]. On the other hand, several studies have not found hypertriglyceridemia to be an independent risk factor for ischemic stroke, or a week, inconsistent association was found between fasting TG levles and ischemic stroke, while others demonstrated a strong linear association between fasting TG levels and cerebral ischemia [24-26].

Although the debate remains whether TG is an independent risk factor for ischemic stroke, with compelling evidence on both sides of the discussion, several large studies demonstrated benefit of decreasing TG level with subsequent decrease in coronary heart disease events, and decreased mortality and strokes [27,28]. VAHIT study and its subsequent analysis suggest that Gemfibrizole can decrease the incidence of TIA in men with coronary heart disease, and ischemic stroke ischemic stroke in men with coronary heart disease and low HDL- C, with a major suggestion that decreasing TG levels, independent of decreasing LDL- C, was responsible for this risk reduction [29].

Regardless of the various analyses, TG remains a risk factor for ischemic stroke, whether indirectly, or independently. Apheresis has been utilized for the prevention of pancreatitis in patients with hypertriglyceridemia, especially in the presence of other organ dysfunction [30-32]. In our patient the severe persistent headache, especially in the setting of peripheral vaso- occlusive disease, was concerning for impending stroke, and plasmapheresis was utilized for rapid control of TG in plasma, after failure of conventional therapy with IV Insulin to lower the TG levels significantly, or to relief the patient symptoms. The symptoms resolved after decreasing TG level below 800 mg/dl (below the cut off level of severity. The patient was discharged with recommendations for long term TG therapy as well as follow up to reassess for recurrence of symptoms or re- elevation of TG levels

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