Management of hypertriglyceridemia induced acute pancreatitis and therapeutic plasmapheresis : Report of nine cases and review of literature

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Abstract

Hypertriglyceridemia is one of the rare causes of the acute pancreatitis. The prevalance of hypertriglyceridemia has increased recently due to the changing eating habits, sedentary lifestyle, alcohol consumption, obesity and concomitant diabetes mellitus. Therefore, the frequency of the acute pancreatitis due to hypertriglyceridemia may increase in coming years. Diagnosis of the acute pancreatitis by hypertriglyceridemia can be overlooked easily and may be very severe if untreated accurately on time. In addition to the standard management of pancreatitis, specific treatment for hypertriglyceridemia that is insulin, heparin and anti-hypertriglyceridemic drugs are used. Therapeutic plasmapheresis is the last treatment option and seems the most effective one in this subject through developing device and membrane technologies when we review the current literature. Not only triglycerides but also proinflammatory cytokines and adhesion molecules that play an active role in pathogenesis are removed by plasmapheresis. So, the effectiveness of treatment appears promising. However, the exact pathophysiology of hypertriglyceridemia-induced pancreatitis could not be fully understood and the majority of published experience comes from the case reports and the benefit of randomized clinical trials is not available. Therefore, there are no data about what are the exact indications and when we start therapeutic plasmapheresis in literature. This manuscript describes our hospital experience with treatment options and analyzes reports published recently about plasmapheresis as a treatment modality for hypertriglyceridemia induced acute pancreatitis. (Acta gastroenterol. belg., **2017**, 80, **71-74**).

Key words : Hypertriglyceridemia, acute pancreatitis, therapeutic plasmapheresis

Introduction

Acute pancreatitis is an inflammatory disorder of the pancreas and it may be represented by a variety of different clinical conditions ranges from mild pancreatic edema to severe necrosis that may lead to death. The clinical picture may also vary from a self-limiting mild form of pancreatitis to very severe conditions that may progress to death with serious complications including dehydration, metabolic imbalance, hypotension and sepsis. Hypertriglyceridemia (HTG) is an important but frequently neglected cause of acute nonbiliary pancreatitis. It is responsible for 1-4% of all cases of pancreatitis (1). Acute pancreatitis also may be seen in 12-38% of hyperlipidemic patients. There is a risk of acute pancreatitis if the triglyceride (TG) level is higher than 500 mg/dL, however the frequency of pancreatitis is much higher when the level exceeds 1000 mg/dL (2). Since mild and moderate elevation of TG level may be seen in 30% of the cases with acute pancreatitis, other causes should be ruled out before the diagnosis HTG induced acute pancreatitis.

Cases

A total of 9 cases who were hospitalized and treated with diagnosis of HTG induced acute pancreatitis in Antalya Training And Research Hospital Internal Medicine and Gastroentrology Clinics in 2014, were evaluated. Laboratory analyses, abdominal ultrasound and MR- cholangiography (MRCP) were performed in all patients. The bedside index for severity in acute pancreatitis (BISAP) score was used to identify the severity of pancreatitis. 2 patients, who did not recover in their follow-up and required plasmapheresis, underwent abdominal computed tomography (CT). Other causes of acute pancreatitis have been excluded in all patients except for HTG**.** All of the patients' characteristics are seen in Table 1.

The mean age of cases was 38.1 years and 2 of them were female while 7 of them were male. The mean period of hospitalization was 6.5 days. Only 1 patient did not present with comorbidity (2nd case on the table), however his blood glucose level was high in his follow-up and he was diagnosed with type-2 diabetes mellitus (DM). All of the other patients have one or more diseases in their past medical history as seen in the table. 2 patients had diagnosis of isolated hyperlipidemia (HL) before hospitalization but they were not on treatment. One of the patients only had DM (5th case on the table), but he also hadn't been on treatment for 2 months. None of the medications the patients used caused increased risk for acute pancreatitis.

2 of the patients were using alcohol (5th and 9th cases on the table), however they were social drinkers and the etiology was not considered to be related

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to alcohol. BISAP scores of 5 cases were 0 and the remaining were 1, so patients were considered to have mild acute pancreatitis. The standard management of the acute pancreatitis comprising fluid resuscitation and pain management was performed to all patients. Insulin, subcutaneous low molecular weight heparin and oral fibrate treatment were initiated to treat HTG. Antibiotic therapy was not administered to any patient. 2 patients (3rd and 7th cases on the table) not responding to these treatment strategies underwent therapeutic plasmapheresis (TPE) successfully. These patients were;

The 3rd case on the table was a 29 year-old housewife. She was the patient that stayed at the hospital for the longest period, 10 days. She told us that she had been told to have hypercholesterolemia before, but had not been prescribed any medication except for diet and exercise. She also hadn't applied to any physician for 2 years. The TG level was 1214 mg/d and BISAP score was 1 at presentation. No other etiology was detected and she was also diagnosed as acute pancreatitis due to HTG, and the treatment was started. On the 3rd day of her follow-up, her pain decreased, TG level receded to 723 mg/dL, amylase- lipase levels reduced and oral intake was permitted. After initiation of oral intake abdominal pain became evident and her TG level increased to 1510 mg/dL again. Levels of amylase and lipase increased approximately 2 folds. CT of abdomen revealed no pathology except enlargement in pancreas size and peripancreatic fluid collection. On excluding biliary etiology by MRCP, TPE was performed on the 4th day of hospitalization. She underwent plasmapheresis for 3 times because of elevated TG levels and continuing pancreatitis. After 3rd session her complaints resolved and TG decreased to 637 mg/dL (57.8% reduction). Oral intake was permitted slowly by fat-free and only liquid foods. No complications related to pancreatitis were observed in her control abdominal ultrasonography. Becoming clinically stable she was discharged on the 10th day of hospitalization. She was prescribed fibrate, statin medications and recommended diet besides exercise for HTG.

The 7th case on the table was 33 year-old male, he was on treatment with subcutaneous insulin aspart three times daily, subcutaneous insulin glargine and rosuvastatin tablet once a day, with diagnoses of type-1 DM and HL. His TG level was 1349 mg/dL at presentation and he hasn't been detected to have any other etiology, so he was evaluated as acute pancreatitis due to HTG. His BISAP score was 1. The classical and specific treatments mentioned above were administered to the patient. The pain occuring in the epigastric region and radiating to the back continued with decreasing severity at the 48th hour of hospitalization. His TG level was 1150 mg/dL and amylase-lipase level was 4 times higher than the normal limit. The abdominal ultrasonography taken again was normal apart from the pancreatic heterogeneity. TPE was performed 2 times on the 3rd and 4th days of hospitalization without any complications. His TG level receded to 453 mg/dL (60.6% reduction) in his follow-up and the clinical picture improved rapidly. The patient was discharged healthy by ordering outpatient treatment on the 8th day of hospitalization.

After the recovery of clinical picture of pancreatitis, laboratory parameters and vital signs, HL and other comorbid diseases of all cases were prescribed. Finally, all patients were discharged with recommendation of diet, exercise and policlinic control after 4-6 weeks.

Discussion

A total of 153 cases present with acute pancreatitis were followed in our Internal Medicine and Gastroenterology Clinics in 2014. HTG was detected as an etiology in 9 of these patients with a frequency of 5.8% which is slightly higher than the literature. The increment of the prevalance of HL can be expected recently especially due to the rise in the frequency of DM and obesity, widespread fast food consumption, sedentary lifestyle and alcohol abuse. Among our patients only 1 did not have a remarkable medical history, however he was diagnosed with DM in his follow-up. Other cases had DM, HL or both. Only 2 patients had been given a diagnosis of isolated HL before hospitalization. A primary lipid disorder may also exist in a few of the patients and the risk for pancreatitis is higher especially in type-1, 4 and 5 (2). The mean age of these patients was lower (38.1 years) according to the biliary pancreatitis patients (56.3 years).

HTG induced acute pancreatitis presents with epigastric or right upper quadrant pain radiating to the back, nausea, vomiting, anorexia, fever, and jaundice as in the cases with other etiologies. Patients may have signs such as eruptive xanthomas and lipemia retinalis in physical examination and milky plasma suggesting HTG. Since these patients may have normal serum lipase and amylase levels, diagnosis of pancreatitis may be overlooked, therefore amylase and lipase levels of the patients with probable diagnosis is acute pancreatitis should be analyzed on diluted serum. Although the inflammation begins in pancreas, it may turn to a systematic form due to the release of cytokines, toxins and hydrolytic enzymes (3). Based on multifactorial etiology of the disease, various scoring systems are used to determine the severity and prognosis of the disease. We evaluated the patients with BISAP score and the lowest score was 0 and the highest one was 1.

The management of acute pancreatitis consists of hydration, regulation of the electrolyte imbalance, sufficient analgesia, antibiotherapy if needed and the etiology-specific therapy if the underlying cause is known. Insulin, heparin, anti-hypertriglyceridemic drugs and TPE are treatment options that can be used in the management of acute pancreatitis due to HTG (2). Heparin and insulin enhance chylomicron degradation by increasing lipoproteinase activity and, thus decrease the toxic effect of free fatty acids on acinar cells of pancreas (4). Fibrates are the first drugs which are

Table 1. — **Patients characteristics. (BISAP: The bedside index for severity in acute pancreatitis, M:male, W:women, TG:triglyceride, DM: diabetes mellitus, HT: hypertension, HL:hyperlipidemia, COPD: chronic obstructive pulmonary disease)**

Case number	Age (year)	Sex	TG (mg/dL)	BISAP score	Co-morbidity	Hospitalization (day)	Pancreatitis attacks number
1	36	M	1461	0	HL	5	First attack
2	44	M	1412	1	DM (newly diagnosed)	7	First attack
3	29	W	1214	1	HL	10	First attack
4	43	M	923	0	DM, COPD, HL	7	Second attack
5	47	M	1353	1	DM	4	First attack
6	37	W	1217	1	DM, HL	7	Second attack
7	33	M	1349	0	Type-1 DM, HL	8	First attack
8	34	M	865	0	DM, HL	6	First attack
9	40	M	1159	0	DM, HT	5	Second attack
Mean	38.1		1217			6.5	

prefered orally to reduce serum TG concentration and should be initiated if the patient can tolarate. Statins, nicotinic acid and omega-3 fatty acids may be added to the treatment carefully with regard to adverse effects if HTG is resistant (2).

Apheresis is the general name of the process in which a specific component of the blood is separated and removed, the remainder of the blood returned to the patient and has been used since 1944 to safely collect plasma, plasma components, or cells from donor blood (5).TPE is a subtype of apheresis and a procedure in which blood of the patient is passed through a medical device which separates out plasma from other components of the blood, the plasma is removed and replaced with a replacement solution such as colloid solution (e.g., albumin, plasma) or combination of crystalloid/colloid solutions (6). Albumin has been used in most reports and plasma in some of them as it contains LPL and could enhance TG removal as a replacement solution. No direct comparisons of replacement fluids have been reported (6). It is achieved either by continuous blood centrifugation or by cross-flow filtration of blood with artificial microporous membranes which have 0.2-0.6 mm maximal pore size. Centrifugal methods have greater removal because of the tendency of the TG to clog the pores of the filters (6). A large volume of plasma is removed at a flow rate of 10-60 mL/min. Duration of the procedure is different from patient to patient and an average plasma exchange procedure lasts about 2 hours. Not only triglycerides but also proinflammatory cytokines and adhesion molecules that play an active role in pathogenesis are removed by plasmapheresis. In addition to this apheresis improves insulin sensitivity and glycemic control. TPE is a very safe and an effective method, however urticaria, hypotension, headache, shivering and catheter-related problems are rare complications (7). 2 important contraindications for plasmapheresis include bleeding tendency and hypersensitivity to heparin (8).Successful TPE requires a reliable venous access, which may be either 2 large, durable peripheral veins, or a central venous catheter with a dual lumen that is rigid enough to withstand significant flow and pressures. The apheresis treatment should be administered by the attending physician of the patient and the apheresis physician according to the pathological substance that is being removed, and by the desired endpoint (9).

Generally apheresis is used therapeutically for the treatment of autoimmune, metabolic, and hematologic disorders when the pharmacological treatment is ineffective. It is also a therapeutic option in HTG and HTG induced acute pancreatitis if standard management methods are inadequate to control disease (10). However, the efficiency and indications of plasmapheresis in HTG induced acute pancreatitis is still not clear yet due to the lack of well organised randomised controlled trial evaluating this issue. Reductions in TG level in literature after TPE is very variable and decrease of TG up to 90% has been reported in different series (6, 9, 10, 11, 12, 13). American Apheresis Society (ASFA) conducted a literature review to evaluate the rationale for plasmapheresis in HTG induced acute pancreatitis in 2010 (14). This review is consistent with the findings of studies by Chen et al. (11) and Gubensek et al. (12), and reported no randomised controlled trial while evaluating the effectiveness of plasmapheresis in these patients. According to this, ASFA has categorized the use of TPE in HTG induced acute pancreatitis as a Category III indication, which implies that the optimum role of apheresis therapy in these patients is not established due to limited data and conflicting reports (14). ASFA highlights the role of clinicians in making individualized decisions due to the weak evidence in this subject. Besides the lack of absolute indications, the timing of the apheretic treatment is also controversial (11). Many reports specify that maximal reduction in morbidity and mortality can be achieved when apheresis is used as early as possible (15). Some authors have recommended that it should be used if there is no improvement with standard therapy (9). 7 of 9 patients (77.7%) improved with

standard treatments while 2 youngest patients (22.2%) of our cases (cases 3rd and 7th) have been started TPE at the 3rd and 4th days of their hospitalization because of having not responded to the initial standart therapy. 2 sessions TPE were performed to one patient and 3 sessions to the other one, and their clinical status and labarotary parameters improved rapidly without any complications. Consequently, TPE is an effective therapeutic modality and plays an important role in the urgent treatment of life threatening HL cases, such as pancreatitis (16). Gelrud et al. suggest that TPE may be applicable if serum TG level is greater than 1.000 mg/dL plus lipase level 3 folds over the upper limit of normal and signs of lactic acidosis, hypocalcemia, or signs of worsening inflammation or organ dysfunction and if there are no contraindication to plasmapheresis (1). Due to the inadequate evidence it is reasonable that TPE management should be individualized according to the patient's clinical and laboratory status. Firstly we performed standard and specific treatment modalities (because as there were no organ dysfunction and BISAP score was low in our patients) and observed laboratory results and clinical status of the patients for a few days. Though initial treatments were strictly applied, we started TPE for 2 patients on the 3rd and 4th day of hospitalization because their TG and lipase levels were high and they had abdominal pain. The aim of aphresis is to reduce TG concentration below 500 or 1000 mg/dL (according to patient), lipase level to normal and clinical improvement, if the level of TG is higher than 500-1000 mg/dL and there is organ dysfunction the process can be repeated (7).

Alipogene tiparvovec is a promising but expensive gene treatment applied recently for severe pancreatitis due to LPL deficiency and studies related to this drug are not as yet avaliable (17).

Conclusion

We observed that early diagnosis and treatment of HTG in patients with acute pancreatitis result in a quick recovery of the clinical status. Because, there are different therapeutic approaches including the decrease of TG level for management of pancreatitis due to HTG. Therefore, TG levels of all patients hospitalized for acute pancreatitis should be screened at admission to the hospital and HTG should be considered among reasons. If etiology is HTG specific treatments should be started rapidly. The indication of TPE is determined according to the course of the disease. If there is no clinical improvement with standard management in 2 or 3 days it may be performed. However, TPE may be indicated in early phases in cases of organ dysfunction and highness of any severity index. TPE is an effective alternate modality management, as shown by our experience. But, multicenter trials with large number of patients are needed to document the effectiveness of TPE.

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