Original Article

Observation of Clinical Courseand Response to Conservative Management Inpatients with Hypertriglyceridemic Acute Pancreatitis Admitted to Medical Ward.

Kamran Rashid Mirza and Ambreen Kamran Mirza

Objective: To study the characteristics and clinical course of hypertriglyceridemic acute pancreatitis patients admitted under care of medical department and observed the effects of conservative management on triglyceride levels.

Methods: Patients presenting with mild to moderate acute pancreatitis having admission triglyceride levels more than 11.3mmol/l (1000 mg/dl), normal biliary anatomy and absent gall stones were included. They were closely monitored clinically as well as with serial pancreatic enzymes and triglyceride levels. Initially, the patients were started on conservative regimen including NPO, IV fluids, insulin infusion and anti-lipid medications. Plasmapheresis considered as a non-conservative intervention was not done immediately on admission, but was reserved for the cases showing lack of improvement, worsening of symptoms or lack of reduction in triglyceride levels within 24 to 48 hours of starting treatment.

Results: Twelve patients over the period of five years were studied, including nine males and three females. Diabetes turned out to be main cause of hypertriglyceridemia (nine out of 12 patients were known diabetic, and two were newly diagnosed during this admission). Patients with diabetes were found to be poorly compliant with their treatment and monitoring of blood sugar levels. All patients were either overweight or obese, BMI ranged from 27.8-35.5 Kg/m2. Four patients gave history of alcohol intake and two had hypothyroidism. Five patients were known to be dyslipidemic but none of the patients were aware of any family history of hyperlipidemia. Three patients needed plasmapheresis due to systemic complications and persistent pain whereas, the remaining patients improved with conservative management only. Triglyceride levels declined rapidly and steadily for almost all patients and average time of discharge was approximately one week.

Conclusion: Rising obesity and diabetes can lead to increase in cases of hypertriglyceridemic pancreatitis. Diagnosis can easily be missed if triglyceride levels are not checked on admission, as levels can drop rapidly due to treatment started for acute pancreatitis. Patients should be strongly emphasized for compliance to treatment of diabetes and hyperlipidemia and advised to lose weight to prevent occurrence of these cases.

words: hypertriglyceridemia, acute pancreatitis, hypertriglyceridemic pancreatitis.

Introduction

Acute pancreatitis (AP) is a common and potentially fatal medical condition.[1] Hypertriglyceridemia is frequently associated with AP, both either as a precipitant or as anepiphenomenon. While mild to moderate elevations are found in up to 47% of cases, it is the severe hypertriglyceridemia that has been described to cause AP.[2] Up to 7% of AP could be due to severe hypertriglyceridemiaand it is accepted as third most common cause after gall stones and alcoholism.[3] There is a suggestion that hypertriglyceridemic pancreatitis (HTGP) is associated with higher severity and complication rates,[4] but it is not agreed by all.[5] The increasing prevalence of hypertriglyceridemia due to the changing eating habits, sedentary lifestyle, alcohol consumption, obesity and concomitant diabetes mellitus can lead to increased frequency of the acute HTGP in future.[6] Bulk of the literature indicates that triglyceride level (TGL) of at least 11.3mmol/l (1000mg/dl) are required to cause pancreatitis.[7] Some other studies indicate requiring even higher levels.[2]

High levels of serum triglyceridecan be result of either genetic factors or secondary causes or in most cases involving both. In Frederickson Classification of hyperlipidemias types I, IV and V can lead to hypertriglyceridemia. Types I and V can by themselves lead to very high levels, whereas type IV in addition requires secondary causes to be present.[8]

Secondary causes in addition to those mentioned above also include drugs like tamoxifen, estrogens etc.[8]

It is advised to reduce TGL below5.65 mmol/l [500 mg/dl] to alleviate symptoms and prevent recurrences.[9] The standard treatment of AP includes Intravenous fluids (IVF) and nothing per oral (NPO), this also helps in reducing TGL. Multiple treatment strategies available to treat severe hypertriglyceridemiaincluding anti-lipid drugs like fibrates and omega 3 fatty acids, heparin and insulin infusions, and more aggressive methods like plasmapheresis and lipid apheresis.[10] The treatment to reduce triglycerides should be started as early as possible and usually more than one treatment options are used. Plasmapheresis is expensive, hazardous and is not available widely. Some studies have shown early use of plasmapheresis associated with better outcome.[10] American Society for Apheresis (ASFA) guidelines recommend plasmapheresis as category III grade 2C in acute HTGP.[11] The purpose of our study was to see the effects of conservative management on the clinical course and TGLof patients with acute HTGP and to reserve plasmapheresis only for those cases not showing improvement. In our hospital standard international units (mmol/l) are used. In this study units in metric system (mg/dl) are also given where necessary.

Methods

We collected twelve cases of acute HTGP from December 2012 to March 2018. The study was conducted at the Department of Medicine, Al-Adan Hospital, Kuwait. The diagnosis of AP was basis on Revised Atlanta Classification 2012.[12] The severity was judged into mild, moderately severe and severe AP also based on Revised Atlanta Classification. The inclusion criteria were age greater than 18 years, admitted to medical ward with AP of mild to moderate intensity having initial TGL greater than 11.3 mmol/l [1000mg/dl]. TGLs were done on admission for all patients presenting with AP and having normal biliary anatomy and absent gall stones on imaging. Those patients who were on any medication, probable of causing AP including GLP-1 receptor analogs and DPP-4 inhibitors were excluded. Social alcohol drinkers were included as do most studies on HTGP however patient with history of recent heavy alcohol intake were not included. Also the patients who got directly admitted to ICU were not included in the study. All the information was noted on a pre-devised Performa.

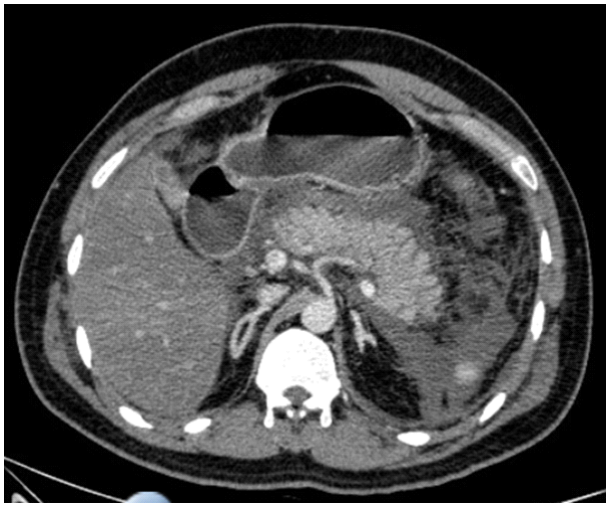
Secondary causes like diabetes, alcohol intake, hypothyroidism, and hyperlipidemia as well as drug history were looked for. Treatment taken by patient including anti-lipid and anti-diabetic medications and there compliance was noted, as well as any drugs that can cause hypertriglyceridemia like estrogens. The physical examination included BMI, search for any local or systemic complications. During the stay in the ward patients were regularly and closely monitored. Serial serum triglyceride, cholesterol, amylase and lipase levels were done alongwith CT abdomen.

As initial management all patients were put on NPO and IVF and received Fenofibrate145 mg once daily (with sips of water). Insulin infusion was planned for patients with hyperglycemia at the rate of 0.05 U/Kg/Hour. Blood sugar was monitored hourly and insulin infusion rate was titrated to maintain target blood sugar levels approximately 6.111mmol/l [110200mg/dl].Insulin infusions were continued for 48 to 72 hours depending upon the condition of the patient. Plasmapheresis was not included as initial treatment and was only to be done if there was lack of improvement, worsening of symptoms or persistently elevated triglyceride levels. Admission TGL was not considered as an indication.

Results

Nine patients were male and three females, five were Arab and seven belonged to Indian Subcontinent. All patients were of younger to middle aged group with mean age of 41.6 years [range 29 to 55 years]. All patients were either overweight or obese, the BMI ranged from 27.8 to 35.5 Kg/m^2 (average BMI; 31.2 Kg/m^2). Type 2 diabetes mellitus was major secondary factor for hypertriglyceridemia present in eleven out of twelve patients. Of these nine were known diabetics whereas two were newly discovered. All diabetic patients had uncontrolled blood sugar readings on admission and received insulin infusions. History of dyslipidemia was found in only five patients. One of these patient was known to have an attack of acute HTGP. She was on fenofibrate and was admitted this time with second attack due to poor compliance of treatment. Other four patient were prescribed statins in past, but no old lipid profile lab results were available with them. All patients confessed to poor compliance of diabetic and hyperlipidemic treatment. Surprisingly none of our patients had any idea about the history of dyslipidemia in their families. Four patients had history of alcohol intake. Only two patients were hypothyroid. All patients were admitted with chief

complaints of vomiting and abdominal pain of varying duration of few days.TGLs on admission ranged from 14.86 mmol/l [1315mg/dl] to 48.28 mmol/l[4272mg/dl] (average: 26.44 mmol/l [2339.8mg/dl]). Lipase was found to be more consistently elevated above the three times normal limit [10 patients] as compared to serum amylase (**see tables)**. Two patients had normal amylase on admission, however their CT scan were suggestive of AP thus fulfilling the revised Atlanta Classification 2012 criteria for diagnosis. Five patients were diagnosed with mild AP and remaining with moderately severe pancreatitis. CT scan was done in all patients except one, who was known case of HTGP, admitted with second attack and refused the scan. The results of CT scan revealed oedematous non-necrotizing pancreatitis in six patients and other five patients having necrotizing pancreatitis [see tables].Transient respiratory dysfunction was noted in one patient (see below), luckily none of our patients deteriorated to develop any permanent organ damage. As noted before all patients were initially put on NPO and started on IVF and fenofibrate whereas eleven patients received insulin infusion. Plasmapheresis was needed for three patients. One of them (pt. no: 1) had developed systemic complications including basal pneumonitis and bilateral pleural effusion with transient episode of desaturation which improved in ICU without need for ventilation. The other two patients [pt. no: 3& 10]had persistent pain in spite of improving TGL. Luckily all patients had rapid fall in their TGLas well as improved clinically post one session of plasmapheresis ruling out the need for any further sessions. Those patients who were managed conservatively showed a progressive drop in TGL (see chart) except one who had an increase in TGL on second day of admission [pt. no: 4], his TGL rose from 19.49 to 25.84 as he was clinically improving and his pancreatitic enzymes were reducing we continued to manage him conservatively and from day three onwards his TGL started to come down. No patient developed any complications that needed prolonged admission. Patient stay ranged from four to 9 days. Our aim was to discharge patients when TGL reach less than 5.65 mmol/l (500mg/dl), however some patients asked for earlier discharge. They were discharged with dietary advice and follow up in OPD.



Pancreatic oedema, peri-pancreatic fluid and phlegmon, particularly around pancreatic tail. CT abdomen picture of patient no: 1

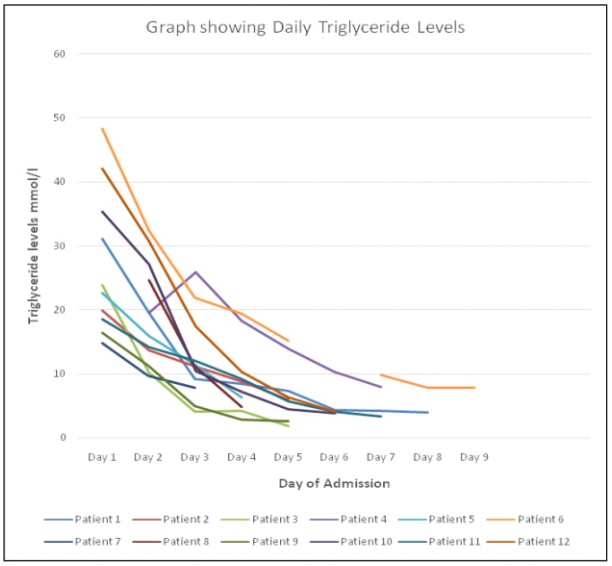


Table-1: Socio-demographic characteristics of the family.

	Patient 1	Patient 2	Patient 3	Patients 4	Patients 5	Patients 6
Age (in years)	31	49	41	35	29	39
Gender	Male	Male	Female	Male	Male	Male
Nationality	Subcontinent	Arab	Arab	Subcontinent	Subcontinent	Subcontinent
BMI [Kg/m2]	3.0.5	28.7	33.2	31.8	32.6	28.1
Alcohol intake	Yes	Yes	No	No	No	No

Diabetes	No	No	Yes	Yes, newly discovered	Yes	Yes
Hypothyroidism	No	No	Yes	No	No	No
Known case of dyslipidemia	No	No	Yes	No	No	No
CT ABD	Non-necrotizing Oedematous pancreatitis with mild free fluid	Oedematous Pancreatitis	Necrotizing pancreatitis, small necrotic foci in pancreatic head	Acute necrotizing pancreatitis, pelviabdominal collection	Oedematous non-necrotizing pancreatitis.	Necrotizing pancreatitis
Triglyceride mmol/l [mg/dl] (on admission)	31.15 [2756]	19.96 [1766]	19.49 [1724]	19.49 [1724]	22.7 [2008]	48.28 [4272]
Total cholesterol mmol/l-[md/dl] (on admission)	13.3 [513]	13.99 [540]	11.29 [436]	18.36 [709]	18.3 [706]	20.25 [782]
Amylase U/L (on admission)	180	66	485	255	613	742
Lipase U/L(on admission)	623	94.8	717.3	482	867	1216
Blood Sugar mmol/l[mg/dl] (on admission)	11.6 [209]	13.4 [241]	14.2 [256]	9.81 [176]	13.3 [239]	14.4 [260]
Plasmapheresis	Yes	No	Yes	No	No	No
Triglyceride on discharge mmol/l [mg/dl]	3.98 [35.2]	6.13 [542.5]	1.91 [169]	7.96 [7.4]	6.3 [557]	7.8 [690]

Table-2: Characteristics and lab results of the patients.

	Patient 7	Patient 8	Patient 9	Patients 10	Patients 11	Patients 12
Age (in years)	44	35	52	43	47	55
Gender	Male	Male	Emale	Female	Male	Male
Nationality	Arab	Subcontinent	Subcontinent	Arab	Subcontinent	Arab
BMI [Kg/m2]	27.8	34.1	31.7	30.9	28.6	35.3
Alcohol intake	No	Yes	No	No	Yes	No
Diabetes	Yes	Yes	Yes, newly discovered	Yes	Yes	Yes
Hypothyroidism	No	No	No	Yes	No	No
Known case of dyslipidemia	Yes	No	No	Yes	No	Yes
CT ABD	Not done refused	Oedematous pancreatitis, peripancreatitic fluid	Oedematous pancreas, no necrosis	Acute necrotizing pancreatitis Pelviabdominal, peipancreatic fluid collection	Oedematous Pancreatitis	Acute Necrotizing Pancreatitis
Triglyceride mmol/l [mg/dl] (on admission)	14.86 [1315]	24.46 [2164]	16.4 [1452]	35.4 [3133]	18..6 [1646]	42.1 [3726]
Total cholesterol mmol/l-[md/dl] (on admission)	9.43 [349]	11.22 [433]	9.7 [375]	14.2 [548]	12.4 [479]	17.4 [672]
Amylase U/L (on admission)	184	157	210	187	92	394
Lipase U/L(on admission)	702	520	411	592	107	1017
Blood Sugar mmol/l[mg/dl] (on admission)	15.5 [279]	11.1 [200]	17.2 [310]	16.7 [301]	18.4 [332]	13.9 [251]
Plasmapheresis	No	No	No	Yes	No	No
Triglyceride on discharge mmol/l [mg/dl]	4.57 [404]	2.78 [246]	2.55 [226]	3.8 336]	3.3 [292]	4.1 [363]

Discussion

Our study shows that most patients with mild to moderate HTGP can be managed conservatively with plasmapheresis reserved only for selected cases. Our study was limited by smaller number of patients and the fact that it did not include patients with severe pancreatitis who are usuallyadmitted directly to ICU. High TGL could be primary (genetic), secondary or both. We didn't have means to study the genetic defects, however searched for secondary causes of hypertriglyceridemia.Forston et al in a study of seventy five patients described poorly controlled diabetes as most common association with hypertriglyceridemic pancreatitis followed by alcohol intake.[13] Diabetes was a major risk factor in our patients too. All our patients were either obese or overweight. Alcohol intake and hypothyroidism were other secondary causes for hypertriglyceridemia. No one was taking any drug which would cause hypertriglyceridemia neither did we encounter any pregnant patient. As mentioned before minimum TGL believed to cause pancreatitis is 11.3 mmol/l (1000mg/dl) and in most cases levels are in excess of 20 mmol/l.[2]In our study the mean TGL at time of admission was 26.44 mmol/l [2339.8 mg/dl]. At these levels there is presence of

chylomicrons in blood which are large TG rich lipoproteinsand have highest capacity of carrying triglycerides in their core.[14] The exact pathogenesis of hypertriglyceridemia induced pancreatitis is still unclear. The proposed mechanisms include hydrolysis of triglycerides in and around the pancreas by pancreatic lipase seeping out of acinar cells leads to accumulation of free fatty acids (FFA) in high concentration. These unbound free fatty acids are toxic and produce injury to acinar cell or capillariescausing inflammation. Chylomicrons induced hyperviscosity leadsto impairment of circulatory flow in capillary beds and ischemia.[8] Genetic predisposition may also play a role. In a review by John Scherer et al potential role of FFA have been further described citing multiple experimental animal and in vitro studies. FFAs cause mitochondrial damage, necrosis via inhibition of mitochondrial complexes I and V and decrease acinar ATP levels. In vitro studies that used orlistat to pharmacologically inhibit pancreatic lipases and block FFA production prevented the injury to acinar cells co-incubated with chylomicrons.[8] Hypertriglyceridemia is frequently an under recognised as a cause of AP.[15] Chylomicrons are rapidly metabolised on fasting instituted as a treatment of AP and in majority of the patients TGLwill fall within 72 hours, hence delay in consideration can lead to failure to diagnose correct etiology. Searles et al recommended to consider chylomicronemia in all patients with AP even in presence of other etiological factor.[15] Even if it is not possible to investigate hypertriglyceridemia in all patients of acute pancreatitis it is strongly recommended to do lipid profile on admission for the patients who have risk factors for hypertriglyceridemia, have normal biliary anatomy on imaging or have lipemic serum. The process of lowering TGL can be further accelerated by adding anti-lipid drugs known to cause reduction in TGL like fenofibrate which is considered as first line medication for treatment of hypertriglyceridemia[16] as well as insulin infusion. Our observations have also shown steady decline in TGL upon starting treatment. (Graph)The diagnostic criteria of AP includes at least three times elevated pancreatic enzymes. In absence of this clinicians rarely consider this diagnosis. However the levels of pancreatic enzyme levels can be spuriously low when TGL are higher than 5.65 mmol/l [500mg/dl], possibly due to interference with the assay.[8] This can be corrected with serial dilutions. Fortson et al noted elevations in serum amylase and lipase greater than 2 times normal in 54% and 67% cases respectively.[13] In our study three times above normal elevation for serum amylase was found in only four patients [33%]whereas for serum lipase in ten patients [83%].Two patients presented with normal serum amylase levels on admission. Therefore patients of HTGP may not meet this diagnostic criterionand it requires to maintain a high level of suspicion of HTGP in appropriate clinical setting and the confirmation of diagnosis should be done by imaging.

Lipoprotein lipase (LPL) is responsible for removing chylomicrons from blood.[17] Deficient LPL activity is noted in patients with hypertriglyceridemia. Insulin and heparin infusions have shown to enhance the activity of LPL. In diabetic patients insulin infusion should be used to enhance reduction in TGLas well as to maintain euglycemia. Insulin infusion have shown to be helpful even in non-diabetic patients.[17] All our patients received insulin infusion except one(pt; 1). We did not considered heparin infusion in our patients as its role is still controversial. Its effects on raising LPL levels are usually transient followed by markedly decreased LPL activity and accumulation of chylomicrons.[17] However there are studies where heparin and insulin infusions were used together successfully.[17]Direct and rapid removal of chylomicrons can be achieved by lipopheresis or plasmapheresis. Lipopheresis was not available to us. Numerous studies have documented the effectiveness of plasmapheresis in hypertriglyceridemia with[6] or without pancreatitis.[18] Plasmapheresis is an expensive treatment, not free from hazards[6] and may not be widely available. However it is very reliable methods to achieve lower TGL. A single session of plasmapheresis can lower TGL up to 70%.[19] Three of our patients received plasmapheresis. All of them were having moderately severe pancreatitis and needed just one session. However it may be noted that patient suffering from severe pancreatitis may need more than one sessions. Some algorithms[20] suggest to consider plasmapheresis if TGL above 11.3mmol /l(1000mg/dl) however in our study we have seen this is not necessary as most patients even with much higher TGLcan do quite well without it. Based on our study we suggest that its use should be individualized.

Conclusion

Number of HTGPcases may rise in future as the risk factors like diabetes and obesity are on rise. Diagnosis can easily be missed or delayed if high level of suspicion is not maintained. Patients with no clear

cause of pancreatitis on admission should have their TG levels done especially if they are obese or have diabetes. Early diagnosis and prompt treatment of hypertriglyceridemia will lead to lesser complications and improved outcome. Multiple treatment options should be used to treat hypertriglyceridemia. Plasmapheresis where available and affordable can be used on individualized basis. To prevent further attacks compliance to treatment of diabetes and hyperlipidemias should be strongly emphasized. Weight loss and adherence to healthy lifestyle needs to be encouraged and proper education provided in this regard.

Department of Medicine,
Al-Adan Hospital Kuwait
www.esculapio.pk

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