Clinical Study of 224 Patients with Hypertriglyceridemia Pancreatitis

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Abstract

Background: Hypertriglyceridemia (HTG) is the most common etiology of acute pancreatitis (AP) after alcohol and gallstone-induced disease. Elevation of serum triglyceride (TG) levels to ≥ 1000 mg/dl in a patient with AP strongly indicates HTG as the cause. The absolute risk of pancreatitis based on serum TG ≤ 1000 mg/dl has not been clearly defined. The aims of this study were to address the role of elevated TG levels between 500 and 1000 mg/dl in the clinical course of HTG pancreatitis (HTGP); and assess the relationship between the level of serum TG and disease severity.

Methods: A total of 224 HTGP patients between 2007 and 2011 were divided into two subgroups. Totally, 122 patients in Group A had serum TG >1000 mg/dl; 102 patients in Group B had maximal TG levels between 500 and 1000 mg/dl accompanied by lactescent serum; 100 patients with biliary AP and 99 patients with alcoholic AP hospitalized during the study period were enrolled as controls. The clinical and biochemical data were analyzed.

Results: The clinical presentation of HTG-induced pancreatitis was similar to other causes. Severe form of AP in Group A was higher than Group B ($\chi^2 = 4.002$, $P = 0.045$). The severity with HTGP was significantly higher as compared to biliary AP ($\chi^2 = 33.533$, $P = 0.000$) and alcoholic AP ($\chi^2 = 7.179$, $P = 0.007$). Systemic complications with HTGP were significantly higher than biliary AP ($\chi^2 = 58.763$, $P = 0.000$).

Conclusions: The study demonstrated that TG level ≥ 500 mg/dl should raise a high degree of suspicion, especially if no other etiology of AP is apparent. The severity of HTGP seems to correlate directly with TG level. HTGP seems be more severe than other causes of AP.

Key words: Acute Pancreatitis; Clinical Features; Hypertriglyceridemia

INTRODUCTION

An association between lipid metabolism and pancreas was noted many years ago. The appearance of lactescent serum during an attack of acute pancreatitis (AP) was first recognized by Speck in 1846.[1] Hypertriglyceridemia (HTG) is a well-established cause of AP, accounting for 1–4% (as high as 7%) of patients who present with AP.[2-4] HTG may be primary in origin or secondary to alcohol abuse, uncontrolled diabetes, pregnancy/oral estrogen, or use of drugs.[5] The exact mechanism by which HTG causes AP has not been fully elucidated.[6] One hypothesis is that pancreatic lipase hydrolyses excess triglyceride (TG) causing accumulation of free fatty acids in the pancreas. Free fatty acids in turn cause acinar cell and pancreatic capillary injury. The resultant ischemia creates an acidic environment, which further enhances free fatty acid toxicity. Another hypothesis is that hyperviscosity due to elevated levels of chylomicrons in the pancreatic capillaries leads to ischemia.[7-9] HTG has been shown to contribute to and accelerate the inflammatory cascade in animal models of AP.[9] A recent study by Chang *et al*.[10] has identified specific genes associated with HTG pancreatitis (HTGP).

The natural history of patients with HTGP depends on how effectively the serum TG level and concomitant secondary risk factors are controlled.[11] Since the clinical presentation often mirrors pancreatitis from other etiologies, recognition of HTG as a cause or contributing factor for AP is often delayed or completely missed. Also, it is unclear whether HTGP is more severe than other causes of AP.[2,11]

Elevation of serum TG levels to ≥ 1000 mg/dl or ≥ 11.3 mmol/L in a patient with AP strongly indicates HTG as the cause.[12,13] HTG <500 mg/dl should not be incriminated as a factor in the etiology of pancreatitis.[2] TG level between 500 and 1000 mg/dl accompanied by lactescent serum (chylomicrons are formed at TG levels >500 mg/dl, which makes the serum milky in color) should raise a high degree of suspicion, especially if no other obvious etiology of AP is apparent or when estimation of TG has been delayed.[2,14] However, there is little evidence in the literature on the characteristics

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of AP in patients with HTG levels between 500 and 1000 mg/dl. The absolute risk of pancreatitis based on serum TG ≤1000 mg/dl has not been clearly defined.[11] Clinical studies assessing the impact of HTG on the severity of AP have also shown conflicting results.[15-19]

This retrospective study was undertaken to address the role of elevated TG levels (between 500 and 1000 mg/dl) on the clinical course of HTGP; assess the relationship between HTG levels and disease severity; and compare the clinical features of HTGP with alcoholic AP and biliary AP.

METHODS

Study population

This retrospective study included 224 patients with a clinical diagnosis of HTGP in seven hospitals in Beijing during 5 years, from January 1, 2007 to December 31, 2011. Cases were included if they met the following criteria:[20,21] (1) Clinical presentation consistent with AP; (2) elevated amylase and lipase levels or evidence of pancreatitis by ultrasound and abdominal computed tomography (CT) imaging; and (3) serum TG levels ≥1000 mg/dl, or TG levels between 500 and 1000 mg/dl accompanied by lactescent serum in the absence of other causes of pancreatitis, such as gallstone disease, alcoholism, trauma, etc.[2,14] The patients were divided into two subgroups. Group A included 122 patients with TG levels ≥1000 mg/dl. Group B included 102 patients with TG levels between 500 and 1000 mg/dl accompanied by lactescent serum. A total of 100 patients with biliary AP and 99 patients with alcoholic AP hospitalized during the study period were enrolled as controls.

The clinical and biochemical data of all study participants were recorded on standardized forms. Their clinical course was evaluated using the following criteria: Ranson's criteria,[22] Acute Physiology and Chronic Health Evaluation II (APACHE II),[23] and Balthazar CT severity index scores.[24] Severe AP was diagnosed if the patient presented with one of the following conditions:[20] (1) Local complications (pancreatic necrosis, pancreatic pseudocyst, or pancreatic abscess); (2) organ failure; (3) Ranson's criteria ≥3; or (4) ≥8 APACHE II points.[25]

Statistical analysis

Results are reported as percentages (%) or mean ± standard deviation (SD). Comparisons were performed using one-way ANOVA or Student's t-test for continuous variables and χ^2 test for qualitative variables. Multiple linear regressions were performed to estimate the association between the TG level and the severe AP. Statistical significance was judged at $P < 0.05$. All statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) for windows.

RESULTS

Between 2007 and 2011, 224 patients with HTGP (174 men and 50 women) were referred for investigation. The patients were divided into Group A and Group B. About 54.5% of the patients in Group A had serum TG >1000 mg/dl. About 45.5% of the patients in Group B had maximal TG levels between 500 and 1000 mg/dl. None of the patients had a history or evidence of gallstones or alcohol abuse. Table 1 shows the clinical features of the two subgroups. There was no statistically significant difference in the sex ratios (males: 79.5% and 75.5%) between the two subgroups ($P = 0.129$). The patients had typical symptoms of AP, including abdominal pain (99.2% and 99%), nausea/vomiting (64.8% and 88.2%), and fever (21.3% and 18.6%). The average age of patients in Group A was found to be significantly higher as compared to Group B ($P = 0.000$). About 56.5% of patients (69/122) in Group A and 43.1% of patients (44/102) in Group B presented with the severe form ($P = 0.045$). About 13.9% of patients in Group A and 14.7% of patients in Group B had recurrent pancreatitis ($P = 0.869$) [Table 2]. Between the two groups, 13 (10.66%) and 12 (11.76%) patients were experiencing their second episode; four (3.28%) and three (2.94%) patients were experiencing their third or more episodes. There was one death each in Group A and Group B. All other patients were cured.

Table 3 shows the complications developed by all the study patients with HTGP. In the two subgroups, pancreatic necrosis was found in 10 (8.20%) and 10 (9.80%) patients, followed

Table 1: Characteristics of patients with HTGP in two subgroups

Variables	TG ≥1000 mg/dl, n = 122 (54.5%)	TG ≥500 mg/dl and ≤ 1000 mg/dl, n = 102 (45.5%)	χ^2 or t	P
Males, n (%)	97 (79.51)	77 (75.49)	2.299	0.129
Age, years, mean ± SD	44.22 ± 10.31	43.48 ± 10.03	47.399	0.000
Abdominal pain, n (%)	121 (99.18)	101 (99.02)	–	1.000*
Nausea/vomiting, n (%)	79 (64.75)	90 (88.24)	16.535	0.000
Fever, n (%)	26 (21.31)	19 (18.63)	0.247	0.618
Severe form, n (%)	69 (56.56)	44 (43.14)	4.002	0.045
Length of stay, days, mean ± SD	16.25 ± 11.57	17.68 ± 19.35	15.523	0.000
Patients with recurrent, n(%)	17 (13.93)	15 (14.71)	0.027	0.869
Death, n (%)	1 (0.82)	1 (0.98)	–	1.000*

*Fisher's exact test. SD: Standard deviation; HTGP: Hypertriglyceridemia pancreatitis; TG: Triglyceride.

Table 2: Number of recurrences in patients with HTGP, n (%)

Number of recurrences	TG ≥1000 mg/dl (n = 122)	TG ≥500 mg/dl and ≤ 1000 mg/dl (n = 102)
0	105 (86.07)	87 (85.297)
1	13 (10.66)	12 (11.76)
2	2 (1.64)	0 (0)
3	0 (0)	2 (1.96)
4	1 (0.82)	1 (0.98)
5	1 (0.82)	0 (0)

HTGP: Hypertriglyceridemia pancreatitis; TG: Triglyceride.

by pancreatic pseudocyst (7.38% vs. 6.86%), metabolic disturbances (54.10% vs. 43.14%), acute respiratory distress syndrome (9.84% vs. 10.78%), acute renal failure (3.28% vs. 3.92%), acute hepatic failure (1.64% vs. 1.96%), shock (1.64% vs. 0.98%), and arrhythmic heart failure (1.64% vs. 1.96%). There were no statistically significant differences in local complications ($P = 0.824$) and systemic complications ($P = 0.082$) between the two subgroups. However, there was no significant correlation between TG levels and local or systemic complications (data not shown).

Laboratory readings of 224 patients with HTGP at the time of admission are shown in Table 4. In all patients, serum TG measured on the 1st day of hospitalization tended to be the highest. The levels of serum pancreatic enzyme were moderately increased, and there was a significant difference between the two subgroups. Amylase levels were three times higher than normal in 23.8% of patients in Group A and 18.6% of patients in Group B ($P = 0.149$). Glucose levels were higher than normal, but there was no statistically significant difference between the two groups. Serum calcium levels at admission were normal or near normal in the patients of both groups.

We also analyzed the characteristics of HTGP as compared to biliary AP and alcoholic AP [Tables 5 and 6]. A significantly

higher proportion of men had alcoholic pancreatitis (97/99, 97.98%) and HTGP (174/224, 77.68%). The age of the patients had no statistically significant difference during the three groups ($P > 0.05$). The TG levels in the HTGP were significant higher as compared to the patients in the biliary AP ($P = 0.006$) and alcoholic AP ($P = 0.000$). All patients had typical symptoms of AP, and the clinical presentation of HTG-induced pancreatitis was similar to other causes. Severe form of HTG AP were significantly higher than the other two groups ($P = 0.000$). Systemic complications of HTG AP were significantly higher than biliary AP ($P = 0.000$). There were no significant differences in the duration of hospitalization and the recrudescence rate between the different etiology groups ($P > 0.05$). Amylase levels were three times higher than normal in 21.43% of patients in the HTGP group but were significantly lower than the biliary AP (76%) ($P = 0.000$).

Discussion

We retrospectively investigated the clinical features of HTG-induced AP and compared its characteristics with biliary AP and alcohol-induced AP. Our study analyzed the clinical characteristics of the patients with HTGP, and the data showed that there were no significant differences in admission findings, majority of the initial laboratory data, local and systemic complications and outcomes between the two subgroups. The severity of AP was higher in the Group A patients. Further correlation analysis showed that there was no relationship between TG levels and patients with severe AP, amylase, complications, and APACHE II and Ranson's criteria scores. The differences could be due to the limitations of the study, such as the small sample size and its retrospective design. The study demonstrated that TG level ≥500 mg/dl should raise a high degree of suspicion, especially if no other etiology of AP is apparent. The severity of HTGP seems to correlate directly with TG level.

It is now widely accepted that serum TG levels >1000 mg/dl can precipitate an attack of AP though some studies have shown higher values.[26,27] Recognition of HTG as a cause for AP is often delayed or completely missed, especially for mild to moderate elevations in serum TG. Our data indicate that the cut-off of 1000 mg/dl appears arbitrary. TG level ≥500 mg/dl should raise a high degree of suspicion, especially if no other obvious etiology of AP is apparent. Additional studies are needed to further characterize the risk of pancreatitis with TG levels <1000 mg/dl.

AP has several causes, and HTG is the most common etiology of AP after alcohol and gallstone-induced disease.[2,14] Our study also compared the clinical features of HTGP with that induced by gallstones or alcohol. Symptoms of HTGP are similar to AP caused by other etiologies. The severity of AP was found to be higher in the HTGP group. The average TG level on admission was significantly higher in patients with HTGP ($P < 0.05$). Another limitation of our study is that we did not investigate the etiology of HTG, such as reviewing

Table 3: Complications of patients with HTGP, n (%)

Variables	TG ≥1000 mg/dl (n = 122)	TG ≥500 mg/dl and ≤ 1000 mg/dl (n = 102)	χ^2 or t	P
Local complications	19 (15.57)	17 (16.67)		
Pancreatic pseudocyst	9 (7.38)	7 (6.86)	0.049	0.824
Pancreatic necrosis	10 (8.20)	10 (9.80)		
Systemic complications	82 (67.21)	57 (55.88)		
ARDS	12 (9.84)	11 (10.78)	3.029	0.082
Shock	2 (1.64)	1 (0.98)		
Metabolic disturbances	66 (54.10)	44 (43.14)		
Acute renal failure	4 (3.28)	4 (3.92)		
Acute hepatic failure	2 (1.64)	2 (1.96)		
Arrhythmia heart failure	2 (1.64)	2 (1.96)		

HTGP: Hypertriglyceridemia pancreatitis; TG: Triglyceride; ARDS: Acute respiratory distress syndrome.

Table 4: Initial laboratory values of patients with HTGP

Variables	TG ≥1000 mg/dl (n = 122)	TG ≥500 mg/dl and ≤1000 mg/dl (n = 102)	χ^2 or t	P
Glucose (mg/dl)	13.68 ± 4.65	10.96 ± 4.96	1.149	0.515
Calcium (mg/dl)	2.13 ± 0.73	2.31 ± 2.18	721.428	0.000
Amylase (U/L)	427.66 ± 383.51	412.94 ± 379.79	10.981	0.000
Amylase (U/L) >3 × normal, n (%)	29 (23.77)	19 (18.63)	2.083	0.149
Lipase (U/L)	239.27 ± 386.18	311.35 ± 565.59	232.464	0.000

The data were shown as mean ± SD, except for amylase (U/L) >3 × normal. SD: Standard deviation; HTGP: Hypertriglyceridemia pancreatitis; TG: Triglyceride.

Table 5: Characteristics of the HGTP compared with biliary AP

Variables	HTGP (n = 224)	Biliary AP (n = 100)	χ^2 or t	P
Male, n (%)	174 (77.68)	47 (47)	29.989	0.000
Age, years, mean ± SD	43.89 ± 10.17	66.82 ± 15.68	0.868	0.669
Abdominal pain, n (%)	222 (98.21)	97 (97)	2.020	0.173
Nausea/vomiting, n (%)	169 (75.45)	72 (72)	0.431	0.512
Fever, n (%)	45 (20.09)	23 (23)	0.617	0.492
Severe form, n (%)	113 (50.45)	14 (14)	33.533	0.000
Local complications, n (%)	36 (16.07)	10 (10)	2.092	0.148
Systemic complications, n (%)	139 (62.05)	16 (16)	58.763	0.000
Patients with recurrent, n (%)	34 (15.18)	14 (14)	0.076	0.783
Length of stay, days, mean ± SD	16.90 ± 15.58	16.50 ± 14.68	0.367	0.249
Death, n (%)	2 (0.89)	2 (2)	–	0.590*
TGs, mg/dl, mean ± SD	1436.28 ± 1262.83	108.85 ± 106.19	0.914	0.006
Amylase, U/L, mean ± SD	420.96 ± 381.04	1587.57 ± 1296.79	2.038	0.733
Amylase (U/L) >3 × normal, n (%)	48 (21.43)	76 (76)	87.151	0.000

*Fisher's exact test. SD: Standard deviation; Biliary AP: Biliary acute pancreatitis; HTGP: Hypertriglyceridemia pancreatitis; TGs: Triglycerides.

Table 6: Characteristics of the HGTP compared with alcoholic AP

Variables	HTGP (n = 224)	Alcoholic AP (n = 99)	χ^2 or t	P
Male, n (%)	174 (77.68)	97 (97.98)	20.949	0.000
Age, years, mean ± SD	43.89 ± 10.17	46.59 ± 9.97	0.625	0.909
Abdominal pain, n (%)	222 (99.11)	98 (98.99)	0.010	0.919
Nausea/vomiting, n (%)	169 (75.45)	53 (53.54)	15.337	0.000
Fever, n (%)	45 (20.09)	20 (20.2)	0.001	0.981
Severe form, n (%)	113 (50.45)	34 (34.34)	7.179	0.007
Local complications, n (%)	36 (16.07)	18 (18.18)	0.220	0.639
Systemic complications, n (%)	139 (62.05)	47 (47.47)	5.974	0.015
Patients with recurrent, n (%)	34 (15.18)	8 (8.08)	3.058	0.080
Length of stay, days, mean ± SD	16.90 ± 15.58	15.56 ± 13.99	0.983	0.147
Death, n (%)	2 (0.89)	0	–	1.000*
TGs, mmol/L, mean ± SD	16.23 ± 14.27	3.34 ± 6.73	0.316	0.000
Amylase, U/L, mean ± SD	420.96 ± 381.04	484.79 ± 544.97	5.396	0.001
Amylase (U/L) >3 × normal, n (%)	48 (21.43)	24 (24.24)	0.314	0.575

*Fisher's exact test. SD: Standard deviation; Alcoholic AP: Alcoholic acute pancreatitis; HTGP: Hypertriglyceridemia pancreatitis; TGs: Triglycerides.

patient medications, medical history, or obtaining a detailed family history to look for familial hyperlipidemia.

We found that the mean TG level (265 mg/dl) of patients with alcohol-induced AP was higher than the upper limit of normal range, which is a moderate elevation of TG according to the criteria proposed by the Endocrine Society.[28] Since mild to moderate elevations in TG are seen in the early phase of AP of any etiology in up to 47% of the cases,[29] it is unclear whether HTG is an epiphenomenon or if it is a cause or contributing factor for AP.[5] The role of HTG in causing AP in alcoholics is also somewhat controversial.[12] Our study revealed that HTG results from AP, and the data showed that the elevation of HTG levels ≤500 mg/dl should not be incriminated as a factor in the etiology of AP. These findings agree with the study of Fortson *et al*.[2]

We found that the average amylase levels were two times higher than normal, and amylase elevations of more than three-fold the upper limit of normal range were noted in

only 21.43% of the patients in the HTGP group, which is significantly lower than that of biliary AP. Cameron *et al*.[14] suggested that hyperlipemic serum could interfere with the amylase determination *in vitro*, or an inhibitor of amylase could be present in the serum of these patients. Serial dilutions of the serum amylase sample can reduce the TG interference.[30] So in view of normal serum amylase levels in these patients on admission, the diagnosis is based on presentation consistent with AP and ultrasound or CT imaging. Clinicians should routinely test TG levels in patients who present with AP to accurately identify the need for specialized management.

Once HTG is established as the cause of AP, restricting TG level to ≤500 mg/dl can effectively prevent the recurrence of pancreatitis.[14] There are no definitive guidelines for severe HTGP therapy. The treatment plan must be tailored to each patient.[6,31] Diet, lifestyle changes and control of secondary factors are key to the treatment, and lipid-lowering drugs

are useful adjuncts in the long-term management of TG levels.[32] In our study, two patients died from pancreatic necrosis while all other patients were cured. Serum TG levels rapidly declined with fasting. Almost 50% of the patients were given oral lipid-lowering drugs. Lipid was avoided when total parenteral nutrition was administered. Apheresis was not performed on any patient.

In conclusion, we describe the clinical features of 224 HTGP patients in our study, and highlight that a high proportion of AP induced by HTG levels between 500 and 1000 mg/dl should not be delayed or missed. Larger, multicenter, appropriately powered trials are needed to further characterize the role of elevated TG levels between 500 and 1000 mg/dl in the clinical course of AP, and the risk of pancreatitis. Future studies should address the mechanism of HTGP.

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