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HYPERTRIGLYCERID-ASSOCIATED ACUTE PANCREATITIS: CLINICAL CHARACTERISTICS AND TREATMENT RESULTS

Abstract*. The aim of the study is to evaluate the clinical characteristics of patients with hypertriglyceride associated acute pancreatitis. A single-center observational study of a series of cases was performed on the basis of the Kyiv Department of Surgery for Liver, Pancreas and Bile Tracts named after V.S. Zemskov in the period from 2018 to 2019. Investigation includes patients with acute pancreatitis and hypertriglyceridemia (the triglycerides level is more than 1.7 mmol/l). Exclusion criteria: patients with acute pancreatitis with normal triglyceride levels, patients with acute pancreatitis with elevated triglycerides, that have not been treated enough. All patients were evaluated by Charlson index of comorbidity, body mass index, alcohol history, relapses and severity of disease. All patients were monitored throughout inpatient treatment, from hospitalization to discharge to home or death. The end point of the study was the discharge of the patient to home after the elimination of the manifestations and complications of acute pancreatitis or death of the patient. The 234 patients who were hospitalized and treated with a diagnosis of acute pancreatitis, 27 patients had hypertriglyceridemia and 3 of them were excluded from the study. The study involved 24 patients. Therefore, the frequency of acute pancreatitis associated with high triglycerides was 11.5% (27/234), with the average level of triglyceridemia was 10.1 ± 2.4 mmol / l (range 5.8 - 13.6 mmol / l) , 75% of patients (18/24) had moderate hypertriglyceridemia (2.3 - 11.2 mmol / l), 25% (6/24) - severe (11.2 - 22.4 mmol / l) . The median age was 32 years (quarterly interval 31.5 - 35 years). There were 18 men (75%) and 6 women (25%). Alcohol-induced pancreatitis was observed in 17 (70.8%) patients with hypertrtiglyceridemia. The median body mass index is 28.9 kg / m 2. Normal weight was 33% (8/24) patients, excessive - 25% (6/24), obesity I stage - 29% (7/24) obesity II stage - 8% (2/24) obesity III stage - 4% (1/24). The Charlson comorbidity index ranged from 0 to 5 points, in 1 patient it was 5 points, in 3 patients - 2 points, in 3 patients - 1 point. Diabetes mellitus were in 25% of patients (6 /24), two of them was diagnosed at first. Recurrent cases of disease were in 58.3% of patients (14 /24), 10 of 14 had a history of two cases of acute pancreatitis. In 71% (17 /24) observed a light stage of the disease, 25% (6 /24) - pancreatitis medium degree of severity and in 4% (1 /24) of the patient severe pancreatitis. Mortality was 4%. Conclusions. The frequency of hypertriglyceride-associated acute pancreatitis is*

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11.5%. In light, moderate and severe pancreatitis, the average degree of hypertriglyceridemia (blood triglycerides 2.3 -11.2mmol/l) was prevailed. Hypertriglyceride-associated acute pancreatitis has no specific complications, but has a tendency to recurrence. Patients with hypertriglyceridemia need constant laboratory monitoring (determination of triglycerides), pharmacological therapy and follow-up to prevent the development of acute pancreatitis.

Key words: acute pancreatitis, hypertriglyceridemia, recurrent pancreatitis, diabetes mellitus, severe pancreatitis.

Introduction. Acute pancreatitis (AP) remains an urgent problem of surgical pancreatology. The results of its treatment depend on the severity of the disease, which depends on various factors not directly related to the disease, but on the principle of mutual abuse is involved in shaping the body's response to pancreatic lesions. Timely detection and elimination of the cause of the disease have a positive effect on the outcome of treatment of patients with AP (Dronov OI, Kovalskaya IO, Gorlach AI, Lubenets TV 2019) Hypertriglyceridemia is proved and is the one of the major 's reasons for AP development. (Balachandra, S.,et al. 2006) Hypertriglyceride-associated pancreatitis is on the third place of AP and has 5 - 10% of alcoholic and biliary genesis. (Pothoulakis I.,et al 2020a) (De Pretis N., Amodio A. and Frulloni L. 2018a) Hypertriglyceridemia - is raising of triglycerides level (TG) in the blood serum with a value of 1.7 mmol / L or more. Union of endocrinologists proposed classification of hypertriglyceridemia: light weight - rate TG - 1.7 - 2.2 mmol / L; moderate - 2.3 - 11.2 mmol / l ; severe - 11.3 - 22.4 mmol / l; very severe hypertriglyceridemia - >22.5 mmol / L (Berglund L.,et al 2012a)The reasons for TG level increase in blood are various and indicate a violation of lipoprotein metabolism. There are primary and secondary dyslipoproteinemias. According to the Frederickson's classification primary (genetic) lipid metabolism abnormalities lead to elevated TG levels lead to lipoproteinemia IV (endogenous hyperlipidemia) and V (familial chylomicronemic syndrome) (Fredrickson D.S. 1965) Alcohol consumption, obesity, insulin resistance, oral estrogen intake are secondary factors in increasing blood TG levels (Carr, R. A.,et al 2016a) (Valdivielso, P., Ramírez-Bueno, A., & Ewald, N. 2014a) In addition to the development of AP, disorders of lipid metabolism are the proven risk factor for cardiovascular disease, diabetes (Ding Y.et al 2019a) (Li X., et al 2018a) In turn, polymorbidity, due to metabolic disorders in patients with AP, has an unfavorable prognostic value as a factor that reduces adaptation to stress. Timely clinical recognition of hypertriglyceride-associated AP is important to identify the group of patients with adverse factors associated with impaired lipid metabolism. The aim of our study was to characterize the clinical course of hypertriglyceride-associated AP and to identify hypotheses for further research.

Materials. Design - single-center observational study of a series of cases. The course and results of treatment of hypertriglyceride-associated AP were evaluated. Criteria for inclusion - patients who were hospitalized for surgical indications with urgent indications with abdominal pain and increased serum amylase more than three times (90 U / l and more) and hypertriglyceridemia. Hypertrigylceridemia was considered to be a serum TG level greater than 1.7 mmol / l. The blood TG level was determined in all patients with AP on the day of hospitalization. The study was conducted on the basis of the Department of Surgery of Liver, Pancreas and Bile Ducts named after VS Zemskov in the period from 2018 to 2019. Exclusion criteria: patients with AP who were transferred from other medical institutions later than 7 days or more after the onset of the disease. Exclusion criteria: patients with AP with normal TG levels, patients with AP and with elevated TG levels who were not treated (refused treatment or transferred to other medical institutions).

During hospitalization, all patients with hypertriglyceride-associated pancreatitis evaluated variables that potentiate the severity of the disease, namely: their comorbid condition, body weight, age, sex of patients, the fact of alcohol

consumption and recurrent course of AP. The comorbid state was determined by the Charlson comorbidity index, body weight - by body mass index (BMI). If a blood glucose level of 7 mmol / l or more was recorded during hospitalization and subsequently, which required correction, in the absence of a history of diabetes mellitus, this condition was assessed as previously diagnosed with diabetes mellitus. The severity of the disease, according to the Atlant 2012 criteria, was determined by the presence of persistent (more than 48 hours) or transient (less than 48 hours) multiorgan failure (MOF), which indicated respiratory, cardiovascular, cerebral, renal, hepatic dysfunction, which were assessed by Marshall scale. Local complications were diagnosed using instrumental imaging methods - ultrasonography and computed tomography. Acute peripancreatic fluid and acute necrotic accumulations indicated the presence of pancreatic necrosis in the first 4 weeks of the disease, after the 4th week such indicators were limited to necrosis (walled-off necrosis) and pseudocysts. Mild disease was characterized by the absence of local and systemic complications, moderate disease had local complications and transient organ dysfunction, severe - in addition to local complications, had systemic complications, manifested by persistent MOF. Infectious complications were diagnosed based on the results of a positive culture obtained by bacteriological examination of the substrate of local complications of AP (aspirate of liquid parapancreatic clusters, pseudocysts or removed pancreatic necrosis). Basic therapy was performed for all patients, and for signs of MOF - treatment in the intensive care unit, with the development of infectious complications used the technique of «step up». All patients were monitored throughout inpatient treatment, from hospitalization to discharge to home or death. The end point of the study was the discharge of the patient from the hospital after the elimination of the manifestations and complications of AP or the death of the patient.

Results. There were 234 patients who were hospitalized and treated with a diagnosis of AP during this period, hypertriglyceridemia had 27 patients (11.5%), 3 patients were excluded from the study due to refusal of treatment and inability for definitive analyze its results. So, 24 patients participated in the study. The median time from the time of illness start was 28 hours (interquartile range of 22 - 48 hours). The median level of amylasemia was 142 U / l (interquartile range 120 - 170 U / l), (reference value up to 30 U / l). The average level of triglycerides in the research group was 10.1 ± 2.4 mmol / L. The interval was 5.8 - 13.6 mmol / l. Severe triglyceridemia had 6 patients (25%), moderate - 18 (75%), mild triglyceridemia was not recorded. The median age of patients was 32 years (interquartile range 31.5 - 35 years). There were 18 men (75%) and 6 women (25%). Alcohol consumption preceded the development of AP in 17 (70.8%) patients with hypertrtiglyceridemia. In 7 (29.2%) AP, was not associated with alcohol consumption. The median BMI was 28.9 kg / m^2 (interquartile range 22.7 - 31.9 kg / m^2). According to BMI, patients with hypertriglyceride-associated AP were distributed as follows: 8 patients (33%) were normal weight, 6 (25%) were overweight, 7 were I stage obesity (29%), 2 were II stage obesity (8%), and III stage -1 (4%). The range of Charleson's comorbidity index ranged from 0 to 5 points, of which in 1 patient it was 5 points, in 3 patients - 2 points, in 3 patients - 1 point and in 19 patients - 0 points. Metabolic syndrome was observed in 5 patients with hypertriglyceride-associated AP, of which 2 women had sclerocystic ovary syndrome. Six patients had diabetes mellitus, 2 of them were diagnosed for the first time. And 14 out of 24 patients (58.3%) had a recurrent course of the disease, with 4 patients having one case of pancreatitis, 10 patients having 2 cases of AP. According to the severity of the disease in 17 patients there was a mild course of the disease, in 6 - AP of moderate severity and in 1 patient had severe pancreatitis.

Patients with mild AP were hospitalized in a general surgical hospital, the average level of TG was 10.7 ± 2.1 mmol / l, moderate hypertriglyceridemia was observed in 13 of 17 patients, severe in 4 of 17. All patients underwent conservative basic therapy. Hypertriglyceridemia normalized on 3 - 5 days of inpatient treatment under the influence of infusion therapy. The comorbidity index ranged from 0 to 1 (1 point due to diabetes mellitus), BMI averaged 28.2 ± 4.9 kg / m^2. The median duration of inpatient treatment was 6 bed-days (interquartile interval 4 - 8 bed-days).

In patients with moderate hypertriglyceride-associated AP, the average time of hospitalization was 29.3 ± 6.5 hours after the disease. The median BMI was 28.9 kg / m^2 (interquartile range 22.7 - 31.9 kg / m^2). All patients had alcohol-induced AP with an average TG level of 9.5 ± 2.4 mmol / L. Moderate hypertriglyceridemia was observed in 4 of 6 patients, severe - in 2 of 6. All patients with moderate hypertriglyceride-associated AP had local complications and transient MOF (Marshall scale from 2 to 4 points). Necrotic complications were observed in all 7 patients, of which pancreatic necrosis was complicated by infection in 4 patients, all of them underwent operation, using the technique of «step-up», on the 4th week of the disease performed a single-stage necrosequstrectomy, in 3 patients - «open» in 1 - combined laparoscopic and retroperitoneoscopically assisted necrosequstrectomy. One patient developed a low-flow duodenal fistula after the operation, the treatment of which required the installation of a nasojejunal probe after the area of the internal fistula opening and tube feeding. Duodenal fistula was eliminated by conservative measures on the 14th day of the postoperative period. All patients with moderate pancreatitis recovered. The duration of inpatient treatment averaged 23.2 ± 11.8 days.

One patient died on the 14th day of the disease, a 32-year-old patient with a BMI of 36.7 kg / m^2, from the admission department was hospitalized in the intensive care unit 48 hours after the onset of the disease with a diagnosis of acute severe pancreatitis. An attack of pancreatitis was associated with alcohol consumption. In a laboratory study in the first 24 hours, lipemia was determined. The patient underwent 5 sessions of plasmapheresis, the level of blood TG after the first session was 7.9 mmol / l, after the third session - 1.2 mmol / l. On the 3rd day of the disease in connection with the syndrome of intra-abdominal hypertension of the II degree (intra-abdominal pressure 19 mm Hg) were drainaged acute peripancreatic fluid accumulations. Against the background of the progression of respiratory distress syndrome (respiratory index - 98) from the 5th day of the disease was transferred to artificial lung ventilation. The cause of death was generalized complications - MOF 12 points for the Marshall scale (respiratory, cardiovascular, renal, hepatic failure). The autopsy revealed total transmural pancreatic necrosis, parapancreatitis with lesions of the paracollar and pararenal spaces, the mesentery of the small intestine and transversal colon, the cellular spaces of the pelvis.

Discussion. Although the connection between hypertriglyceridemia and AP has been proven at the level of experimental and population studies, there is no consensus in the literature on some issues on this problem: the connection between the degree of hypertriglyceridemia and severity of AP, features of hypertriglyceride-associated AP in comparison with pancreatitis of other etiology, features of alcohol-induced AP with the increased level of TG.

According to studies by the Spanish Union for Atherosclerosis, a patient with severe hypertriglyceridemia (blood TG 11.3 - 22.4 mmol / l) was characterized as a man aged 50-60 with obesity, a smoker who abuses alcohol, suffering from diabetes (frequency of diabetes mellitus is 42.3 - 72% among patients with hypertriglyceride-associated AP). (Scherer J., Singh V., Pitchumoni C.S., Yadav D 2014a)

The level of TG in the blood of more than 11.3 mmol / l is associated with a high frequency of AP. (Balachandra, S.,et al 2006)

The authors also note that the severity of triglyceride-associated AP correlates with the degree of hypertriglyceridemia. (Zhang X.L.et al 2015b) (Scherer J., Singh V., Pitchumoni C.S., Yadav D.2014b)

Our study shows that the frequency of AP associated with high levels of TG is 11.5%, with an average level of triglyceridemia of 10.1 ± 2.4 mmol / l, 25% of patients had severe hypertriglyceridemia, 75% - moderate, mild and severe hypertriglyceridemia were not observed. Most patients were young (median - 32 years). The incidence was predominant in men (75%) and 71% of hypertriglyceride-associated AP was alcohol-induced. Most patients were overweight (median BMI - 28.9 kg / m^2).

According to the results of a multicenter study that covered the countries of North America (458 patients), Europe (377 patients), Latin America (232 patients), Asia (351 patients) found that the proportion of men was 53%, the average age was 48 years (34 - 63 years), BMI averaged 27.6 ±

6.4 kg / m^2, 17.4% of patients had diabetes mellitus, 49.4% consumed alcohol, 65.7% of patients had mild AP, and 16, 8% required treatment in the intensive care unit (Pothoulakis I.,et al 2020)

When comparing the severity of AP on the etiology of X.L. Zhang and co-authors report severe pain in hypertriglycerides of aspirated AP compared to biliary and alcoholic (Zhang X.L.,et al 2015b) (Scherer J., Singh V., Pitchumoni C.S., Yadav D.2014c)

Our study did not compare the severity depending on the etiological differences of the disease, but the study group was significantly dominated by patients with mild AP (17 cases out of 24), moderate AP - 6 cases out of 24, severe AP was observed in one case. At the same time, in patients with mild, moderate and severe AP, moderate hypertriglyceridemia prevailed.

High incidence of hypertriglyceridemia is also associated with diabetes mellitus (including newly diagnosed) (De Pretis N., Amodio A. and Frulloni L. 2018b)

The mechanism of hypertriglyceridemia on the background of insulin resistance occurs under the influence of free fatty acids, from which the liver synthesizes very low density lipoproteins. The incidence of diabetes in our study was 6 cases out of 24 and it is this nosological unit caused the comorbid background in patients with AP.

Regarding the recurrent course, according to the results of our study, the frequency was 58% (14 out of 24 patients), while 10 out of 14 had more than one recurrence of the disease. This cohort was dominated by young patients (median 29 years), with obesity (BMI - 31.5 kg / m^2), despite their young age, they had a comorbidity index of 2 - 3 points due to diabetes and metabolic syndrome.

The results of the latest multicenter study indicate that recurrent pancreatitis associated with hypertriglyceridemia had patients with a mean age of 41.9 years, mostly men (66%) who were obese (BMI - 30.9 kg / m^2), abused alcohol (67.5 %) and in 51.2% of cases had diabetes (Pothoulakis I.,et al 2020)

Given our data and the results of other centers, we believe that the prospects for further research should be focused on dispensary monitoring of patients with hypertriglyceride-associated pancreatitis and long-term prediction of the manifestations of this metabolic disorder.

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Conclusions.

1. The frequency of hypertriglyceride-associated acute pancreatitis in the overall structure is 11.5%;
2. Moderate trygliceridemia level leads to mild, moderate and severe AP.
3. Hypertriglyceride-associated acute pancreatitis has no specific complications
4. Hypertriglyceride-associated acute pancreatitis has a tendency to recurrent
5. Patients with impaired lipid metabolism and predisposition to hypertriglyceridemia require constant laboratory monitoring (determination of triglyceride levels), medication correction and dynamic monitoring to prevent the development of acute pancreatitis.

Author's contributions: concept, GA and LL; methodology, GA, LL, S.I .; formal analysis, LL, GA; research, GA, LL, S.I., M.O., T.I .; resources, G.A .; data curation, GA, LL, S.I., M.O., T.U; written - original project of preparation, GA, LL, S.I .; review and editing, LL, S.I .;

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