Current concepts of etiology of chronic pancreatitis

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Pancreas is one of the main elements of the digestive-transport conveyor. It synthesizes secretion over 2 liters per day, containing more than 20 digestive (proteolytic, lipolytic, amylolytic, nucleases) enzymes, bicarbonates [2]. The intensity of the secretory process is 20 ml per 1 g of mass of the pancreas (weight it is 80-100 g). At the exit of the final product (secret) per unit of body weight of pancreatic parenchyma productivity is compared to women in the mammary gland of lactating height or with kidneys which produce 1.5 ml of urine per minute. 20% of mass of the pancreas accounts for its enzymes [2]. Obviously, with a decrease of exocrine function of the pancreas and in the absence of substitution polyenzyme treatment, precisely digestion quickly enough and soon suffers, and this is followed by violation of all types of metabolism, i.e. developing of malnutrition syndrome, which consists of a syndrome of impaired digestion (maldigestion) and reduced syndrome absorption (malabsorption) [1, 3].

This issue was dedicated to the scientific meeting devoted to the latest data of pancreatitis and pancreatic exocrine insufficiency, including diagnosis and correction, which took place on June 26, 2013 in Zurich (Switzerland), bringing together a number of participants of the 45th Congress of the European Pancreatic Club in Zurich on June 26-29, 2013.

Professor Markus M. Lerch in the report "The etiology of chronic pancreatitis: genetics, alcohol or smoking?" identified three reasons for the need to allocate different etiologies of chronic pancreatitis: specific treatment; inherent comorbidity; different strategies of cancer-prevention.

He named hyperlipidemia, , associated with deficiency of apolipoprotein II and lipoprotein lipase as the main risk factors for chronic pancreatitis of metabolic etiology. This type of hyperlipidemia is characterized by increased triglycerides over

1000 mg/dl, and it is very rare. The target lowering level of triglycerides is a value less than 500 mg/dl, which helps eliminate symptoms [29]. Hyperparathyroidism also relates to the etiology of metabolic risk factors and leads to an increase in plasma calcium levels that is associated with increased risk of pancreatitis. The incidence of chronic pancreatitis in patients with hyperparathyroidism is 1.5-7.0%. Early parathyroidectomy in these patients is leading to reduction of symptoms of pancreatitis [1, 23].

It is postulated that smoking is an independent risk factor for acute and chronic pancreatitis. It is proved that the risk of developing acute and chronic pancreatitis progressively increases from 1.0 to 4.5 for non-smokers for the hard smokers. Correlation between smoking and the risk of developing pancreatitis is confirmed also by a decrease in pancreatitis risk in smoking cessation [8]. Thus, P. Maisonneuve et al. [7] observed during 16 years 934 patients with chronic alcoholic pancreatitis after diagnosis, tobacco smoking significantly increased the risk of calcification of the gland compared to non-smokers — OR 2,0 [CI 1,1-3,8]. The incidence of pancreatic calcification was 80% versus 40%, respectively ($p<0,0001$).

Essential role of alcohol abuse is known in the prognosis of chronic pancreatitis, pancreatic calcification in patients with non-alcoholic pancreatitis develops much later than in patients with alcoholic pancreatitis [28]. We describe the data of long-term (4 to 11 years) observation of 32 patients with chronic alcoholic pancreatitis, who continued and did not stop drinking alcohol. Although lowering of bicarbonate, lipase, chymotrypsin in pancreatic secretions were detected in both groups, but the degree of severity of this trend in the group of those who did not stop drinking alcohol was significantly higher ($p<0.01$) [10]. According to a meta-analysis of 7 randomized clinical studies in patients with chronic pancreatitis, according to the speaker, the frequency of abdominal pain syndrome in those who stopped drinking alcohol (1-30%) was significantly lower than for those who did not (40-90%).

The speaker cited data of monitoring conducted with colleagues, for 112 families in 14 countries (418 persons): 58 (52%) carried the mutation R122H, 24

(21%) — N29I and 5 (4%) — mutation A16V, 2 had rare mutations and in 21 (19%) lacked PRSS1 mutation. The average time of the first signs of the disease for the R122H mutation was 10 years (CI 95% = 8-12), for the N291 mutation — 14 years (CI 95% = 11-18) and 14.5 years (CI 95% = 10-21) for those without mutations (P = 0,032). For 50 years of age the cumulative risk of exocrine insufficiency amounted to 37,2% (CI 95% = 28,5-45,8), endocrine disease — 47,6% (CI 95% = 37,1-58,1) and for resection of the pancreas due to abdominal pain syndrome — 17,5% (CI 95% = 12,2-22,7%), which is significantly higher than the level of these indicators in other forms of chronic pancreatitis. There is a progressive increase in the risk of pancreatic cancer by 50-70% from the beginning of symptoms, and overall risk of pancreatic cancer was 44,0% (CI 95% = 8,0-80,0) at the age of 70 years [16]. Very interesting is the identification of a large number of families with hereditary pancreatitis, carrying a mutation at codon 122 of the gene of trypsinogen PRSS1 in a limited area of northern Germany near the city of Münster within a 100-kilometer radius, which, obviously, could be due to inheritance from a common ancestor (founder effect) [13].

Accordingly, the factors preventing pancreatic cancer are: smoking cessation and alcohol abuse, elimination of hyperlipidemia, hypercalcemia, prevention and surgical treatment of gallstone disease, elimination of ductal strictures, adequate medical treatment.

A recent study has found that in the presence of chymotrypsin C gene mutation trypsinogen (PRSS1), associated with the classic hereditary pancreatitis (N29I, N29T, V39A, R122C, and R122H), leads to higher autoactivation trypsin and its levels in the pancreas in comparison to wild-type catonic trypsinogen [27]. Early observations of 50 patients with idiopathic pancreatitis showed that 5 of 50 (10%) patients had mutations of catonic trypsinogen gene. Less than 25 mutations were detected in 35% of these patients [26].

In Germany, two mutations in CTRC (p.R254W and p.K247_R254del) were detected in 30 of 901 (3.3%) patients with idiopathic or hereditary pancreatitis, while these mutations in healthy were identified only 21 of 2804 (0,7%) (OR = 4,6 ; CI 95% = 2.6-8.0; P = $1.3x10^{-7)}$. These mutations were detected in 10 of 348 (2.9%)

patients with alcoholic chronic pancreatitis, but only in 3 of 432 (0.7%) patients with alcoholic liver disease (OR = 4, 2, the CI 95% = 1,2-15,5; P = 0,02).

Mutations were also found in 10 of 71 (14.1%) residents of India with tropical pancreatitis, and in healthy people — only about 1 in 84 (1,2%) (OR = 13,6 ; CI 95% = 1.7-109.2 ;. P = 0,0028) Functional analysis of the CTRC variants showed weakening activity and/or reduction of the secretion.

The findings led to the conclusion that the loss of functional alterations of CTRC is a contributing factor to the development of pancreatitis, due to the reduction of its trypsin-degrading activity [22].

In the observation of the French cohort, including 200 people from 78 families, which lasted 6673 patient-years, PRSS1 gene mutation was found in 68% of them, R122H mutation was detected in 78% of cases, and N29I — in 12% of cases and other — 10% cases. The cumulative risk for pancreatic cancer in this cohort was for 50-years-old men 11%, while the age of 75 — 49%, in women cumulative risk value was 8% and 55%, respectively. Moreover, smoking and diabetes were the main risk factors of cancer [17, 18, 21].

Mutations of PRSS1 gene, SPINK1 also detected in 23% of children with idiopathic chronic pancreatitis, 25% of adults with idiopathic and hereditary pancreatitis and 2% in the general population [19], 20% [25] — 44% [30] in tropical calcificating pancreatitis and in 55% of cases upon pancreatogenic diabetes [24].

Professor Markus M. Lerch further analyzed the role of mutations in the CFTR gene, cystic fibrosis transmembrane regulator. Thus, 37% of patients with idiopathic pancreatitis carry at least one mutation in the CFTR allele [9]. There is evidence that the CFTR gene mutation is a risk factor of pancreatitis only in patients without a history of alcohol abuse (19 to 60% of individuals), but not for patients with alcoholic pancreatitis (8.5% of the 72 individuals) [20].

Summing up their own data and other research results, Professor M. Lerch came to the conclusion that the mutation PRSS1 was detected in 10% of patients vs 0 in the general population; SPINK1 — in 15-25% compared to 1-1.6%; CFTR — in

25-30% compared to 10-15%; CTRC — in 5% vs. 1%; CASR — 19% vs. 10%; and 30-45% in the case the mutation is not known at present.

Henry Sarles in 1961 first reported on the subgroup of patients with chronic pancreatitis, with no alcohol abuse history, characterized by increasing levels of gamma globulin in serum [5]. K. Yoshida from Tokyo, along with a team of co-authors, for the first time introduce into clinical practice the term autoimmune pancreatitis in 1995 [6]. Based on the data histology, 2 types of autoimmune pancreatitis are revealed, which signs are [11, 14, 15]:

For type 1:

1. lymphoplasmocytic diffuse infiltration of the lobules of the pancreas, ducts, fatty tissue, blood vessels and common bile duct;

2. obliterating phlebitis;

3. moderate amount of IgG4-positive plasma cells in and around the ducts, in intralobular fibrous tissue and peripancreatic tissue;

4. elevation in plasma levels of IgG4.

For type 2: granulocyte epithelial damage in approximately 45% of patients (more commonly in young women with inflammatory bowel diseases).

Moreover, both types respond to steroid therapy.

In conclusion, the speaker made a number of statements and conclusions.

Hereditary chronic and idiopathic chronic pancreatitis are associated with inherited mutations of trypsinogen, SPINK1, chymotrypsin C, calcium-sensing receptor and the CFTR, and in the future, obviously, will be identified by a larger number of genes.

The pathophysiological effect of these gene mutations has not been studied fully, which determines the need for further experiments.

Correctable etiologic factors of chronic pancreatitis (autoimmune pancreatitis, etc.) must be clearly differentiated from factors that have not been corrected yet, but should be.

In hereditary pancreatitis, smoking cessation reduces the risk of pancreatic cancer.

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The article provides a summary of the report by Professor M. Lerch "Etiology of chronic pancreatitis: genetics, alcohol or smoking?", made at the scientific meeting held on June 26, 2013 in Zurich (Switzerland), and bringing together a number of participants of the 45th Congress of the European Pancreatic Club. Own and published data describing the role of various risk factors for chronic pancreatitis are presented, such as: hyperlipidemia associated with deficiency of apolipoprotein B and lipoprotein lipase II; hyperparathyroidism; smoking; alcohol abuse; genetic factors; a brief history and classification of autoimmune pancreatitis is given.