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Возможности ранней диагностики и прогнозирования осложненных клинических форм хронического панкреатита

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Цель. Улучшение методов диагностики осложненных клинических форм хронического панкреатита (ХП) путем оценки клинического значения полиморфизмов генов катионического трипсиногена (PRSS1), панкреатического секреторного ингибитора трипсина (SPINK1), трансмембранного регулятора кистозного фиброза (CFTR), алькогольдегидрогеназы (ADH) у больных осложненными и неосложненными клиническими формами ХП.

Материалы и методы. Исследование выполнялось на клинической базе кафедры госпитальной хирургии ФГБОУ ВО Рязанский государственный медицинский университет им. акад. И. П. Павлова Минздрава России, Центра хирургии печени, поджелудочной железы и желчевыводящих путей г. Рязани в 2014–2019 гг. Обследовано 108 пациентов обоих полов в возрасте от 25 до 65 лет, 38 из них перенесли хирургическое лечение осложненного ХП, 20 — с осложненным ХП без хирургического вмешательства, 50 — с неосложненным ХП (группа контроля). Проведено сравнительное клиническое исследование с контрольной группой пациентов, одномоментно выполнялось определение генотипа на 1-е и 10-е сут, контроль лабораторных показателей. Выделение ДНК для анализа из лейкоцитов цельной крови с помощью реагента «ДНК–экспресс–кровь» (ООО НПФ Литех, Россия).

Результаты. Полиморфизма гена катионического трипсиногена PRSS1 и гена муковисцидоза-2 CFTR2 выявлено не было, предсказательная ценность указанных полиморфизмов является несущественной. Для полиморфизма гена муковисцидоза-1 CFTR1 отношение шансов 0,444, но без статистической значимости. Среди пациентов с осложненными клиническими формами ХП чаще регистрировалась мутация гена катионического трипсиногена PRSS1 ($\chi2$ = 6,453, p = 0,012) и ADH ($\chi2$ = 14,176, p = 0,001), тогда как для гена CFTR-1 $\chi2$ = 0,873 (p = 0,351), CFTR-2 $\chi2$ не определен, SPINK1 — $\chi2$ = 0,873, (p = 0,351). Показано, что полиморфизмы генов ADH и катионического трипсиногена PRSS1 соответствуют более выраженным структурным изменениям в паренхиме и протоковой системе поджелудочной железы, обуславливают бóльшую вероятность развития осложнений, тяжелого течения заболевания и меньшую эффективность консервативного лечения; полиморфизм гена ADH увеличивает риск развития кистозной формы ХП ($\chi2$ = 5,898, p = 0,016).

Заключение. Определение полиморфизма гена ADH и катионического трипсиногена рекомендуется использовать в комплексной диагностике ХП, при уточнении показаний к хирургическому лечению пациентов с ХП.

Ключевые слова: *хронический панкреатит; полиморфизм генов; диагностика; кисты поджелудочный железы; PRSS1; SPINK1; CFTR; ADH*

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Possibilities of the early diagnosis and prognosis of complicated clinical forms of chronic pancreatitis

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AIM: This study aimed to improve the methods for the diagnosis of complicated clinical forms of chronic pancreatitis (CP) by evaluating the clinical significance of the polymorphisms of the genes of cationic trypsinogen (PRSS1), pancreatic secretory trypsin inhibitor (SPINK1), transmembrane regulator of cystic fibrosis (CFTR), and alcohol dehydrogenase (ADH) in patients with complicated and uncomplicated forms of CP.

MATERIALS AND METHODS: The study was carried out on the clinical base of the Department of Hospital Surgery, Ryazan State Medical University, Center for Surgery of Liver, Pancreas, and Biliary Tract in Ryazan in 2014–2019. A total of 108 patients of both genders aged 25–65 years were examined. Of these patients, 38 were surgically treated for complicated CP, 20 had complicated CP without surgery, and 50 had uncomplicated CP (control group). A comparative clinical study with the control group of patients was performed, and the genotype was simultaneously determined on days 1 and 10 under controlled laboratory parameters. DNA was isolated from the leukocytes of the whole blood by using a DNA-expressing blood reagent (OOO NPF Litekh, Russia) for further analysis.

RESULTS: No polymorphism of cationic trypsinogen PRSS1 gene and cystic fibrosis-2 CFTR2 gene was found. The predictive value of these polymorphisms was insignificant. For the polymorphism of CFTR1 cystic fibrosis-1 gene, the odds ratio was 0.444, but this finding was not significant. Among patients with the complicated clinical forms of CP, mutations were observed in the PRSS1 cationic trypsinogen gene ($\chi 2 = 6.453$, $p = 0.012$) and ADH ($\chi 2=14.176$, $p = 0.001$). Conversely, they were not detected in the CFTR-1 gene ($\chi 2 = 0.873$, $p = 0.351$), CFTR-2 ($\chi 2$ was not determined), and SPINK1 ($\chi 2 = 0.873$, $p = 0.351$). The polymorphisms of the ADH and PRSS1 genes of cationic trypsinogen were associated with more evident structural changes in the parenchyma and ductal system of the pancreas. They also had a higher likelihood of complications, severe disease course, and a lower efficiency of conservative treatment. The polymorphism of the ADH gene increased the risk of the development of the cystic form of CP ($\chi 2 = 5.898$, $p = 0.016$).

CONCLUSION: The polymorphism of ADH and cationic trypsinogen genes should be determined and used for the complex diagnosis of CP to specify indications for the surgical treatment of patients with CP.

Keywords: *chronic pancreatitis; gene polymorphism; diagnostics; pancreatic cysts; PRSS1; SPINK1; CFTR; ADH*

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Chronic pancreatitis (CP) is gaining importance in the general structure of surgical pathology [1]. CP is a chronic disease of the pancreas with a *long course, steady progression with the morphological restructuring of the pancreatic parenchyma and its ducts*. Today, CP is a socially significant disease characterized by rejuvenation and high prevalence, mainly among working-age individuals. It is responsible for their long periods of loss of working capacity or disability [1,2].

According to the statistical collections of the Ministry of Health of the Russian Federation and the report of the surgical service of Center for Surgery of Liver, Biliary Tract and Pancreas, the annual growth in the morbidity with CP in the Russian Federation and the Ryazan region is noted. Also, surgical activity remains at a high level with an emerging tendency to increase the percentage of minimally invasive surgical interventions.

CP is a multifactorial and polypathogenetic disease. It is *a complex of external and internal factors, including genetic ones, which determine the probability of developing CP and the severity of its course*. The timely diagnosis, early detection of CP, and prediction of its course will enable performing radical surgery at the optimal time in patients without decompensation of concomitant somatic pathology and CP complications [2]. Determination of gene polymorphisms is currently widely used in many fields of medicine [3]. Identification of genetic predisposition will permit preventing the clinical manifestation of complicated forms of CP and, possibly, to develop new complex approaches to the diagnosis, prevention, and timely identification of indications for surgical treatment of CP [4,5].

This study **aimed** is to improve the diagnostic methods of complicated clinical forms of CP by assessing the clinical significance of polymorphisms of genes of cationic trypsinogen (PRSS1), pancreatic secretory trypsin inhibitor (SPINK1), a transmembrane regulator of cystic fibrosis (CFTR), and alcohol dehydrogenase (ADH) in patients with complicated and uncomplicated forms of pancreatitis.

MATERIALS AND METHODS

This study was conducted at the Department of Hospital Surgery, Ryazan State Medical University (RyazSMU), Center for Surgery of the Liver, Pancreas, and Biliary Tracts of Ryazan from 2014 to 2019. The patients lived in Ryazan and the Ryazan region.

A comparative clinical study with a control group of patients was conducted. The work was performed in accordance with the Declaration of Helsinki of the World Medical Association «Ethical Principles for Medical Research Involving Human Subjects» amended in 2008, the National Standard of the Russian Federation «Good Clinical Practice–(GCP) GOST R 52379-2005.» The study was approved by the Local Ethics Committee of RyazSMU (2013).

Inclusion criteria: age 18–80 years, signs of CP («definite» or «probable» CP according to the M-ANNHEIM classification), structural changes in the pancreatic parenchyma according to the Cambridge classification, the possibility of taking venous blood to determine gene polymorphisms, and signed informed consent to participate in the study.

Non-inclusion criteria: attack or recurrence of acute pancreatitis, signs of pancreatic necrosis; acute diseases of the gallbladder and bile ducts requiring surgical treatment (acute cholecystitis, choledocholithiasis); gastrinoma of the pancreas (Zollinger–Ellison syndrome); chronic ischemic abdominal syndrome; cirrhosis of the liver regardless of the causes and level of compensation; chronic diarrhea not associated with CP; decompensated concomitant somatic diseases (diabetes mellitus, cardiovascular diseases, chronic kidney disease, others [6]); any malignant neoplasms of the digestive system and other localizations, a history of chemotherapy or radiation therapy; type 1 diabetes mellitus; information about the patient's current participation in any clinical trials.

A total of 108 patients were included in the study. Two groups were formed: the main group (n = 58) comprised patients with complicated clinical forms of CP who underwent or were expected to undergo resection of the pancreas, and the *control group* (n = 50). *Complicated clinical forms* included chronic abdominal pain syndrome, portal hypertension syndrome, obstructive jaundice syndrome, and duodenostasis [7]. The control group included patients with recurrent CP not accompanied by the above complications. Resection interventions were pancreatic resections, according to Frey and Beger, including the Bern modification. All patients were examined *according* to CP examination standards. The clinical and demographic characteristics of the groups are presented in Table 1.

Patients of the main group were divided into two *subgroups*: 1A–patients who had *already undergone* resection and 1B–patients who *were indicated* for radical surgical treatment. However, at the time of the study, the surgery had not been performed for different reasons: patients underwent preoperative preparation and correction therapy for complications and concomitant diseases and refused surgery for personal reasons.

Besides laboratory and instrumental methods included in the examination standards of patients

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Table 1. Clinical and Demographic Characteristics of Studied Groups of Patients with Chronic Pancreatitis

Parameter	1st Group	2nd Group	Total
n	58	50	108
Men, n (%)	49 (84.5)	39 (78.0)	88 (81.5)
Women, n (%)	9 (15.5)	11 (22.0)	20 (18.5)
Age, M ± m, years	44.7 ± 5.1	45.4 ± 3.2	44.6 ± 2.5

with CP [8,9], gene polymorphisms were determined. The genotype was simultaneously determined on the first and tenth days, and the laboratory parameters were taken. Samples used for genetic typing were obtained from whole peripheral venous blood. The material was collected into anticoagulant EDTA-K3 coated vacuum tubes. The DNA was isolated from leukocytes of whole blood for analysis using DNA-express-blood reagent (OOO NPF Litekh, Russia). Then, allele-specific polymerase chain reaction was performed, followed by electrophoresis to separate the amplification products. Two parallel amplification reactions of the isolated DNA were performed using each pair of allele-specific primers. The amplification reaction products were separated using 3% agarose gel. The electrophoresis results were visualized with a 1% solution of ethidium bromide used as a dye. DNA fragments were visualized with ultraviolet radiation at 310 nm wavelength. The fluorescent signal analysis results of each of the samples indicated the presence or absence of each allele in the hetero- or homozygous form. The determination of polymorphisms was performed on the base of the Central Scientific Research Laboratory of RyazSMU. In the amplification reaction, a glow of one or more areas in the ultraviolet spectrum was determined.

For the study, the following polymorphisms were determined: mutations in the PRSS1 (Arg122His) gene of cationic trypsinogen, mutations in the SPINK1 (Asn34Ser) gene of the pancreatic secretory inhibitor of trypsin, mutations in the 1 CFTR (Phe508Del) gene of cystic fibrosis-1, mutations in the CFTR (Gly542Ter) gene of cystic fibrosis-2, and mutations in the (ADH1B Arg47His)(ADH2 * 1/ADH2 * 2) gene of alcohol dehydrogenase.

The obtained results were statistically analyzed using Excel 2016 software (Microsoft, USA), Stat Soft Statistica 10.0 (Stat Soft Inc., USA) on a personal computer in the Microsoft Windows 10 operating system., The mean value (M) and the standard error of the mean (m) were used to describe the signs with normal distribution. The results were recorded as M ± m with 95% confidence intervals (CI). The two groups of patients with a normal distribution were compared using the Student t-test was used, whereas the Mann–Whitney U test was used for patients with a non-normal distribution. The relative parameters of qualitative characteristics (frequencies and proportions) were compared between the two independent groups using the Pearson $\chi 2$ test and Fisher's exact test. The dependence of the probability of an outcome on the presence of a factor was quantified using the odds ratio (OR) with a 95% CI. Differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

All patients were interviewed for the manifestation (the appearance of the first signs of the disease, Table 2). Thus, the duration of the history in first and second group patients did not significantly differ, and neither did the average age of CP manifestation. It should be noted that in patients of both groups, the average age of manifestation was during the working age. The results of the performed genotyping are shown in Table 3.

Significant differences in the Fischer and Pearson criteria for the ADH gene and the highest value of OR were obtained. The authors interpreted this as a positive correlation relationship between the polymorphism of the gene and the risk of developing CP. No polymorphisms of the SPINK1 gene of the pancreatic secretory trypsin inhibitor and the CFTR2 gene of cystic fibrosis-2 were found. The prognostic significance of these polymorphisms was evaluated as insignificant. For polymorphism of the CFTR1 gene of cystic fibrosis-1, OR was 0.444 but was not statistically significant (95% CI: 0,078–2,536).

The study results of polymorphisms of the PRSS1 gene of cationic trypsinogen and the ADH gene of alcohol dehydrogenase were statistically significant, and OR for ADH was maximal. *These polymorphisms have a high degree of reliability and can be used in the*

Table 2. Average Age of CP Manifestation and Average Duration of Disease

Clinical Criteria	Group 1, n = 58	Group 2, n = 50	p
History duration, M ± m, years	4.4 ± 1.9	5.9 ± 1.8	0.57
Average age of CP manifestation, M ± m, years	39.1 ± 2.3	38.4 ± 1.1	0.78

Table 3. Genotyping Results in Patients with Chronic Pancreatitis

	Group 1, n (%)	Group 2, n (%)	p for F-Criterion	p for Criterion $\chi 2$	Pearson Coefficient of Contingency (C)	OR (95% CI)
PRSS1 (R122H)						
Heterozygote	7 (12.1)	0	< 0.05	0.012	0.237	*
Homozygote	51 (87.9)	50 (100)				
SPINK1 (N34S)						
Heterozygote	4 (6.9)	2 (4.2)	> 0.05	0.351	0.09	0.444 (0.078–2.536)
Homozygote	54 (93.1)	48 (96.0)				
CFTR1 (del508)						
Heterozygote	4 (6.9)	2 (4.2)	> 0.05	0.351	0.09	0.444 (0.078–2.536)
Homozygote	54 (93.1)	48 (96.0)				
CFTR2 (Gly542Ter)						
Heterozygote	0 (0)	0 (0)	> 0.05	1	–	*
Homozygote	58 (100)	50 (100)				
ADH (ADH1B*2)						
Heterozygote	21 (36.2)	3 (6.0)	< 0.05	0.001	0.341	8.892 (2.462–32.114)
Homozygote	37 (63.8)	47 (94.0)				

Note: *–calculation of OR is impossible because one value is 0

complex diagnosis of CP and predict its complicated clinical forms. It should also be noted that the obtained results coincide with the information found in the literature of Asian countries.

Forty-five (77.6%) group 1 patients had retention and postnecrotic cysts in the pancreatic parenchyma. Since it is known from the literature that derangement of the structure and function of some proteins and enzymes can lead to autolysis of the parenchyma and formation of cysts, we investigated the potential relationship between gene polymorphisms and the risk of development of the cystic form of CP (Table 4). A statistically significant relationship between gene polymorphism and the risk of developing cystic CP exists only for ADH. Thus, *polymorphisms of the alcohol dehydrogenase gene in a patient increase the risk of developing cystic lesions of the pancreatic parenchyma*. Hence, the results obtained justify the inclusion of gene polymorphism determination in the complex diagnosis of CP (Figure 1).

Table 4. Gene Polymorphism in Patients with Cystic and Non-Cystic Chronic Pancreatitis

Gene Polymorphism	Cystic Form, n (%)	Non-Cystic Form, n (%)	p for $\chi 2$ Criterion	p for Fisher's Criterion	OR (95% CI)
n	45	13	–	–	–
SPINK1	3 (6.7)	1 (7.7)	0.898	> 0.05	1.2 (0.082-9.009)
PRSS1	5 (11.1)	2 (15.4)	0.667	> 0.05	0.688 (0.117-4.038)
CTFR-1	3 (6.7)	1 (7.7)	0.898	> 0.05	1.2 (0.082-9.009)
CTFR-2	0	0	*	> 0.05	*
ADH*	20 (44.4)	1 (7.7)	0.016	< 0.05	9.6 (1.149-80.226)

Note: *– value calculation is not possible

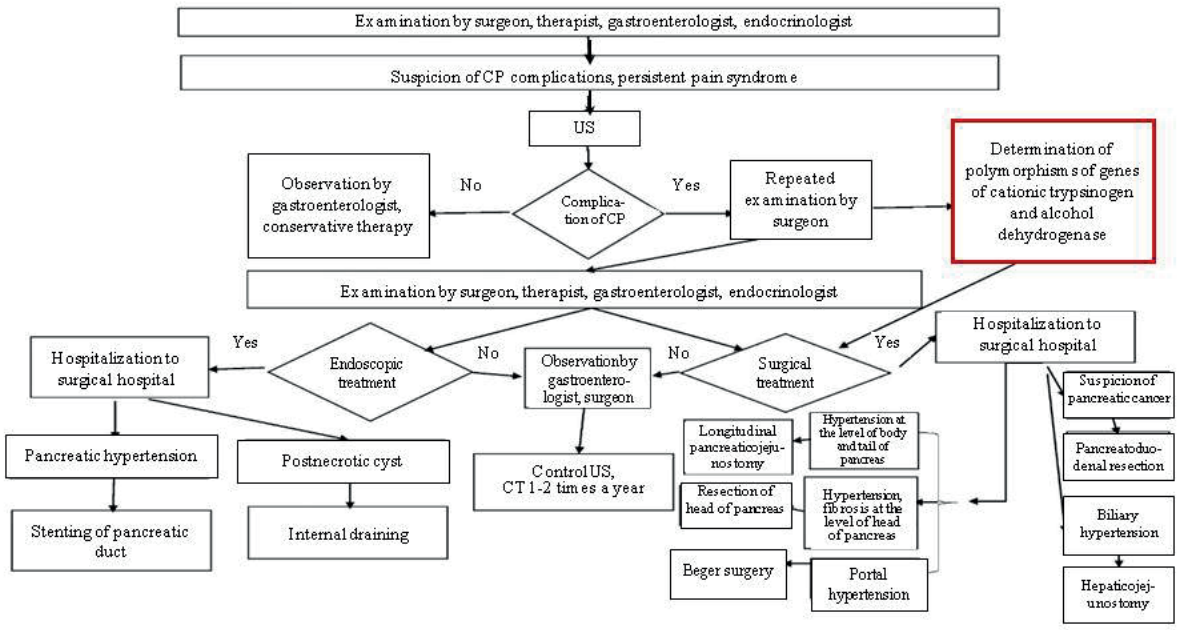

Fig. 1. Place of analysis for gene polymorphism (highlighted) in the algorithm for diagnosing Chronic Pancreatitis.
Note: the presented algorithm is a proprietary development of the team of authors based on the current principles of managing patients with Chronic Pancreatitis.

CONCLUSIONS

1. In the group of patients with complicated clinical forms of chronic pancreatitis, mutations in the cationic trypsinogen gene PRSS1 ($\chi 2 = 6.453$, $p = 0.012$) and the alcohol dehydrogenase gene ($\chi 2 = 14.176$, $p = 0.001$) are more common. For mutations in the CFTR-1 genes for cystic fibrosis-1 ($\chi 2 = 0.873$, $p = 0.351$), CFTR-2 for cystic fibrosis-2 ($\chi 2$ cannot be determined), of the SPINK1 pancreatic secretory trypsin inhibitor gene ($\chi 2 = 0.873$, $p = 0.351$), such regularity was not registered.

2. The alcohol dehydrogenase gene polymorphism significantly increases the risk of developing the cystic form of chronic pancreatitis ($\chi 2 = 5.898$, $p = 0.016$). It enables determining the predisposition to the cystic form of chronic pancreatitis. It justifies observing patient dynamics (ultrasound examination of the abdominal cavity, magnetic resonance cholangiopancreatography, and computed tomography of the abdominal cavity) in two to three months.

3. It is recommended to include the determination of the alcohol dehydrogenase and cationic trypsinogen gene polymorphisms in the complex diagnosis of Chronic Pancreatitis. The results of this analysis should be used to define further indications for surgical treatment of patients with chronic pancreatitis.

ADDITIONALLY

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Participation of authors. *S.V.Tarasenko* — concept and design of the study, statistical processing, *A.A. Natalsky* — design of the study, acquisition and processing of material, *O.D. Peskov* — acquisition and processing of material, *A.Yu. Bogomolov* — research design, text writing, editing, *A.A. Nikiforov* — research design, acquisition and processing of material, *E.O. Avilushkina* — text writing, editing, *P.V. Tarakanov* — writing text, editing.

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