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The Role Of Pancreatic Trypsin Inhibitor (Spink1) Gene Polymorphisms In The Course Of Acute Pancreatitis In The Uzbek Population

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Abstract: This article examines the results of the influence of the SPINK1 (Asn34Ser) polymorphism on the incidence of acute pancreatitis. Environmental factors, in conjunction with genetic factors, play a crucial role in the mechanism of acute pancreatitis development. It was found that there are ethnic differences in the distribution of allele and genotype frequencies of this gene's polymorphic variant. Further development of molecular genetic research through studying the genetic basis of pancreatitis is important for developing new methods of diagnosis and determining treatment strategies with an individualized approach to each patient.

Keywords: Acute pancreatitis, pancreatic trypsin

inhibitor (SPINK1), gene polymorphism.

1.Introduction:

The ongoing increase in acute pancreatitis from 5 to 73.5 cases per 100,000 population puts this disease on the urgent medical and socio-economic agenda. Acute pancreatitis firmly holds the second place (in some regions the first place) among diseases requiring urgent surgical intervention. Complex pathogenesis and insufficiently studied mechanisms of pathological reactions all contribute to a very high mortality rate in patients with acute pancreatitis - up to 30% [1, 2, 3, 4, 7].

Currently, risk factors for the development of pancreatitis are being actively studied due to its global prevalence and socio-economic significance. Large-scale studies conducted by the Framingham study, MONICA, HAPIEE, MERIDIAN-RO, ESSE-RF, and other research centers have identified associations between risk factors and various diseases and conditions in many organs and systems of the human body, as well as assessed socio-economic damage [2, 5, 8].

Due to physicians' low awareness of currently known information on the molecular-genetic basis of pancreatitis pathogenesis, genetic diagnostics of this disease are not being practically implemented in our country. At the same time, according to results obtained in leading laboratories worldwide, at least 6 genes necessary for the development of pancreatitis have already been identified: CFTR, CTRC, SPINK1, CPA1, PRSS1, PRSS2 [1, 6].

A mutation in the pancreatic trypsin inhibitor (SPINK1) gene disrupts the inactivation of trypsin in pancreatic tissues, leading to activation of pancreatic enzymes, proteolytic necrosis of pancreatic tissues, and lysis of venule walls.

The aim of our study was to predict and improve the outcomes of acute pancreatitis treatment by assessing the clinical significance of polymorphisms in the pancreatic trypsin inhibitor (SPINK1) gene.

2. Methods

This study was conducted entirely in the surgical department of Republican Clinical Hospital No. 1 and in the molecular genetics department of RGIAM. To address these issues, we analyzed diagnostic and treatment procedures in 68 patients hospitalized with acute pancreatitis of various etiologies. For the study, we formed age- and sex-standardized groups based on diagnostic and treatment methods. Patients were divided into two groups: - main (n=68), patients with clinical signs of acute pancreatitis; - control (n=70), healthy individuals in whom SPINK1 polymorphism was studied.

The control group consisted of 38 healthy men (n=38) and women (n=32) aged 25 to 66 years (mean age 56.7±8.4). The age of patients in the main group ranged from 29 to 75 years (mean age - 57.3±9.3 years). Of these, 37 (52.2%) were women and 31 (47.8%) were men. Thus, the compared patient groups were matched by sex (main: 37 men, 31 women; control: 38 men, 32 women; $\chi 2$= 0.018, p=0.89) and age (56.7±8.4 and 57.3±9.3; t=0.048, df=146, p=24.17), and these compared groups did not differ significantly in the above indicators ($p<0.05$).

Acute pancreatitis is diagnosed based on the presence of at least two of the following signs, after excluding other surgical pathologies: typical clinical presentation (severe belt-like pain not relieved by antispasmodics, uncontrolled vomiting, history of alcohol consumption, spicy foods or cholelithiasis, etc.). Characteristic ultrasound findings include: enlargement, decreased echogenicity, and indistinct contours of the pancreas; presence of free fluid in the abdominal cavity; hyperenzymemia (hyperamylasemia or hyperlipasemia) exceeding the upper limit of normal by three times or more.

Samples for genetic typing were obtained from peripheral venous whole blood. The materials were collected using vacuum tubes with EDTA-K3 anticoagulant applied to the walls. DNA extraction for analysis of whole blood leukocytes was performed using the "DNA-express-blood" reagent produced in Russia (NPF "Litex" LLC, Moscow). Data analysis was conducted using version 6.0 of the "STATISTICA" statistical package, adhering to the principles and requirements of statistical processing of data in biological and medical research.

3. Results And Discussion

The SPINK1 gene is located on the long arm of chromosome 5 (position 5q32) and consists of 4 exons. It encodes the trypsin inhibitor produced by the pancreas. The physiological function of this protein is to prevent the activation of zymogens catalyzed by trypsin in the pancreas. The SPINK1 gene is expressed in acinar cells, regulates the synthesis and secretion of trypsinogen, and plays an important role in protecting acinar cells and the duct system of the pancreas from damage caused by prematurely activated trypsin.

The study of the SPINK1 (Asn34Ser) gene polymorphism began with an examination of the compatibility of the molecularly genetically studied groups with the Hardy-Weinberg equilibrium. The results of checking the frequency distribution of genotypes in patients with acute pancreatitis and the correspondence of the SPINK1 (Asn34Ser) gene polymorphism to the Hardy-Weinberg equilibrium in the general sample of the Uzbek population matched the expected Hardy-Weinberg equilibrium ($p > 0.05$).

When analyzing the distribution of genotypic and allele frequencies in the general sample of the main patient group, the frequency of the Asn allele was 97%, and the frequency of the Ser allele was 3%. The homozygous Asn/Asn genotype was found in 64 (94.1%) individuals in the main group, and the heterozygous Asn/Ser genotype in 4 (5.9%).

Analysis of the distribution of genotypic and allele frequencies in the control group showed that the frequency of the Asn allele was 99.3%, and the frequency of the Ser allele was 0.7%. Homozygotes for the Asn allele (Asn/Asn genotype) were found in 98.6% (n=69) of individuals, while heterozygotes (Asn/Ser genotype) were found in 1 (1.4%, n=1) individual. The homozygous Ser/Ser genotype was not observed in either the patient group or the control group (Table 1).

Table 1

Analysis of the results from studying the Asn34Ser polymorphism in the SPINK1 gene

Polymorphism		Allele, genotype	Main group (n=68)		Control group (n=70)		Validity
			n	%	n	%	
The Asn34Ser polymorphism of the SPINK1 gene	Allele	Asn	132	97,1	139	99,3	χ^2= 1,92, p =0,17; RR=1,6; OR= 4,2. Risk in Exposed=80%; Risk in Unexposed=48,7%; Overall Risk= 49,3%.
		Ser	4	2,9	1	0,7	
	Genotype	Asn/Asn	64	94,1	69	98,6	χ^2= 1,96, p =0,16; RR=1,7; OR= 4,3. Risk in Exposed=80%; Risk in Unexposed=48%; Overall Risk= 49%.
		Asn/Ser	4	5,9	1	1,4	
		Ser/Ser	0	0	0	0	

Based on Table 1, it should be noted that the study of the Asn34Ser polymorphism in the SPINK1 gene does not reveal a strong role of this gene in the occurrence of acute pancreatitis, both at the genotype level ($\chi2$= 1.96, p =0.16) and at the allele level ($\chi2$= 1.92, p =0.17). However, the relative risk (RR) for genotype and allele is 1.7 and 1.6 times higher, respectively, and the odds ratio (OR) is 4.3 and 4.2 times higher. The risk in exposed individuals was 80%, the risk in unexposed individuals was 48%, and the overall risk was 49%. These results indicate a high risk associated with the Asn34Ser polymorphism in the SPINK1 gene for acute pancreatitis. These indicators are also high in the study of the risk of pancreatic necrosis (Table 2).

Table 2

Influence of the Asn34Ser polymorphism in the SPINK1 gene on the development of pancreatic necrosis in acute pancreatitis

Polymorphism		Allele, genotype	Main group (n=68)		Control group (n=70)		Validity
			n	%	n	%	
The Asn34Ser polymorphism of the SPINK1 gene	Allele	Asn	39	92,9	139	99,3	χ^2= 6,21, p =0,013; RR=3,4; OR= 10,7. Risk in Exposed=75%; Risk in Unexposed=22%; Overall Risk= 23%.
		Ser	3	7,1	1	0,7	
	Genotype	Asn/Asn	18	85,7	69	98,6	χ^2= 6,35, p =0,012; RR=3,6; OR= 11,5. Risk in Exposed=75%; Risk in Unexposed=21%; Overall Risk= 23%.
		Asn/Ser	3	14,3	1	1,4	
		Ser/Ser	0	0	0	0	

The study of the influence of the Asn34Ser polymorphism in the SPINK1 gene on the occurrence of pancreatic necrosis in acute pancreatitis showed that this gene polymorphism predisposes to pancreatic necrosis with high reliability both at the genotype level ($\chi2$= 6.35, p =0.012) and at the allele level ($\chi2$= 6.21, p =0.013).

Additionally, pancreatic necrosis increases the relative risk (RR) and the odds ratio (OR) by 3.6 and 11.5 times, respectively. In this case, the risk in exposed individuals was 75%, the risk in unexposed individuals was 21%, and the overall risk was 23%.

4. Conclusion

Therefore, while the Asn34Ser polymorphism in the SPINK1 gene, unlike the Arg122His polymorphism in the PRSS1 gene, does not significantly affect the overall indicators of acute pancreatitis, it is highly likely to contribute to the development of necrotic changes in the pancreas with high reliability. In conclusion, the article discusses the role of the Asn34Ser polymorphism of the SPINK1 gene in acute pancreatitis. This polymorphism is considered significant in the onset and severe progression of the disease and is highly important for diagnosis and prognosis.

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