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ORIGINAL ARTICLE

Alcohol-metabolizing enzyme gene polymorphisms and alcohol chronic pancreatitis among Polish individuals

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Abstract

Background and aims. Chronic pancreatitis develops in 5–10% of alcohol addicts. In developed societies, alcohol is the cause of chronic pancreatitis in at least 70–80% of cases. The genetic polymorphism of enzymes involved in alcohol metabolism is relevant in the etiopathogenesis of chronic pancreatitis. The aim of the study was to find the ADH, ALDH2 and CYP2E1 alleles and genotypes in the Polish population that are likely to be responsible for higher susceptibility to chronic alcohol pancreatitis. *Material and methods.* We determined the allele and genotype of ADH2, ADH3, ALDH2 and CYP2E1 in 141 subjects: 44 with alcohol chronic pancreatitis (ACP), 43 healthy alcoholics and 54 healthy non-drinkers as the controls. Genotyping was performed using PCR-RELP methods on white cell DNA. *Results.* ADH2*1, ADH3*1 alleles and ADH2*1/*1, ADH3*1/*1 genotypes were statistically more frequent among the patients with ACP than among the controls. The ADH3*2/*2 genotype was more frequent among "healthy alcoholics" and in the controls than among those with ACP. In the studied group, only the ALDH2*1 allele was detected, all patients were ALDH2*1/*1 homozygotic. Differences in the CYP2E1 allele and genotype distribution in the examined groups were not significant. *Conclusion.* In the Polish population examined, ADH3*1 and ADH2*1 alleles may be risk factors for the development of alcoholism. The ADH3*2/*2 genotype may confer protection against ACP. CYP2E1 gene polymorphism is not related to alcoholism and ACP. The Polish population examined is ALDH2*1/*1 homozygotic.

Key Words: *ADH gene polymorphism, alcohol chronic pancreatitis, ALDH gene polymorphism, CYP2E1 gene polymorphism*

Introduction

The abuse of alcohol leads to injury to many organs: the liver, pancreas, gastric mucous membrane and cerebral tissue, and results in the loss of behavior control. In Poland, people treated for alcohol dependency account for about 3% of the population [1]. Chronic pancreatitis develops in 5–10% of alcohol addicts [2], and in developed societies alcohol is the cause of chronic pancreatitis in at least 70–80% of cases [3,4]. Genetic factors are important in the susceptibility to pancreatic injury, severity and evolution of inflammatory processes leading to chronic inflammation or fibrosis. Discovery of the gain of function mutations of pancreatic secretory trypsin inhibitor (SPINK 1) or other potential defects in genes that regulate pancreatic secretory function, or modulate inflammatory response to pancreatic injury (TNF, IL-1, IL-10 genes), has changed the current concept concerning the pathogenesis of pancreatitis. Some few studies indicate that mutations of the cationic trypsinogen gene (PRSS1), cystic fibrosis transmembrane conductance regulator gene (CFTR) and SPINK may also be risk factors for the developing alcohol chronic pancreatitis (ACP) [5–7].

It is known that genetic polymorphism of the enzymes involved in alcohol metabolism has a relevant role in the etiopathogenesis of alcohol liver disease. Several genes encoding ethanol metabolizing enzymes have been proposed and studied in recent years, among them alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH), cytochrome P-4502E1-CYP2E1, glutathione S-transferase M1-GSTM1, GSTT1, with controversial or inconclusive results in people of different races with ACP. It is assumed that this is associated with genetically determined differences in alcohol metabolism. Polymorphic genes ADH1B and ADH1C code different forms of β and γ subunits of different features each. The ADH1B gene occurs in the form of three alleles, ADH2*1,

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ADH2*2 and ADH2*3 responsible for β1, β2 and β3 subunit coding [8,9]. The ADH2*1 and ADH2*2 alleles occur among Caucasians and Asians, ADH2*3 in 25% of the Afro-American population [10], i.e. relatively more often than among the white American, European and Chinese populations [11]. The β1 subunit is barely active in the metabolism of alcohol, while β2 is highly active in this respect.

The ADH3 gene gives two alleles, ADH3*1 and ADH3*2, which code respective subunits γ1 of higher activity and γ2 of lower activity towards ethanol [8,9].

The ALDH2 izoenzyme is the main form of aldehyde dehydrogenase responsible for acetate aldehyde oxidation. The ALDH2 gene has two alleles, ALDH2*1 and ALDH2*2, the latter predominant and typical of Asians and North American Indians and does not occur in Caucasians [12].

Between 10% and 15% of ethanol consumed is metabolized by MEOS [2]. The activity of this system increases as a consequence of long-term ethanol abuse. Alcohol metabolism in individuals who drink regularly causes 5–10 times higher stimulation of MEOS than in individuals who do not drink absolutely or drink sporadically. ADH alcohol oxidation takes place mainly at lower alcohol concentrations in blood, while the peak action of MEOS is observed at high concentrations [8]. The most important enzyme of this metabolic pathway is cytochrome P-450 CYP2E1. The CYP2E1 gene exhibits polymorphism in the 5‘ flanking region of human cytochrome CYP2E1. The CYP2E1 gene forms two alleles – c1 and c2 [13]. The CYP2E1 genetic polymorphism varies significantly among different ethnic groups [14].

The aim of the study was to find the ADH2, ADH3, ALDH2 and CYP2E1 alleles and genotypes in the Polish population that are likely to be responsible for the higher susceptibility to ACP. We studied the frequency of alleles for the ADH2, ADH3, ALDH2 and CYP2E1 genotype in the Polish population when comparing patients with ACP, patients addicted but without pancreas damage or non-drinkers.

Material and methods

Subjects

The study comprised 141 subjects (30 F and 111 M; average age 45.2 ± 9.4 years). The patient group with chronic alcohol abuse included 44 with ACP and 43 alcoholics with no damage to gastrointestinal organs, the pancreas in particular, considered as healthy alcoholics. Fifty-four healthy volunteers, total abstainers, formed a control group.

The chronic alcohol abusers group included patients consuming on average over 80 g of pure ethanol a day over at least 2 years, average 160.9 ± 43.9 g daily. Alcohol history was obtained during a face-to face interview.

All the drinkers examined had a positive CAGE screening test [15] and the patients of the alcoholics group met the DSM-IV diagnostic criteria for alcoholism [16]. They were recruited from the Department of Gastroenterology and from the Department of Therapy of Addiction to Alcohol.

The diagnosis of chronic pancreatitis was based on the generally accepted criteria: medical history, physical examination, abdominal X-ray picture, ultrasound, CT of the abdominal cavity, ERCP and pancreatic exocrine function tests [17]. Twenty-seven patients had ERCP confirming the diagnosis of chronic pancreatitis. In the remaining 27 patients, abdominal X-ray, ultrasound and CT confirmed the diagnosis sufficiently. Calcifications in the area of the pancreas were shown in abdominal X-ray. Ultrasound and CT demonstrated atrophy or diffuse calcification of the pancreas, irregularity and dilated extension of the main pancreatic duct. The alcoholic etiology was defined on the basis of the history.

The alcoholics group underwent examinations to exclude alimentary pathology, particularly of the liver and pancreas. Results of the examinations indicated no organ damage.

The control group comprised healthy volunteers whose histories revealed no consumption of alcohol. Diagnostic tests were performed to exclude any digestive pathology.

All the patients in this study were recruited from the same city and were homogeneity ethnic of the Caucasian race group. The study was approved by a local ethics committee and all subjects gave informed consent for examinations.

Genomic DNA and oligonucleotide

Genomic DNA was isolated from 15 mL of peripheral blood [18].

Genotyping of ADH2 gene polymorphism

For detection of polymorphism in the ADH2 gene, the polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) technique was used on white cell DNA. The primers for amplification were the following: ADH2 247, ADH2 303 and ADH2 290, ADH2 424 and ADH2 352. The amplified product was digested with MaeIII enzyme (Roche Applied Science) and with AluI enzyme (MBI Fermantas) and subjected to electrophoresis in 12% polyacrylamide gel stained with silver nitrate [19].

Genotyping of ADH3 gene polymorphism

Detection of polymorphisms in the ADH3 gene was performed using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP).

The primers for amplification were: ADH3 321 and ADH3 351. The amplified product was digested with the SspI enzyme (MBI Fermantas) subjected to electrophoresis in 3% agarose gel, stained with ethidium bromide [19].

Genotyping of ALDH2 gene polymorphism

Polymorphisms in the ALDH2 gene were detected using the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method. The primers for amplification were ALDH2 YC1 and ALDH2 YC2. The amplified product was digested with EcoRI enzyme (MBI Fermantas) and subjected to electrophoresis in 12% polyacrylamide gel stained with silver nitrate [20].

Genotyping of CYP2E1 gene polymorphism

Detection of polymorphisms in the 5′-flanking region of the P4502E1 gene was performed using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP). The primers for amplification were: CYP2E J8 and CYP2E J9. The amplified product was digested with PstI or RsaI enzyme (MBI Fermantas) and subjected to electrophoresis in 2% agarose gel, stained with ethidium bromide [13].

Statistical analysis

The allele and genotype frequencies between the examined groups were compared using the χ^2 test of association. In the event of too few data, the results were corrected by Yates. $P<0.05$ was considered to be statistically significant. The calculations were performed using the computer statistical program STATISTICA PL [21].

Results

ADH2*1 allele frequencies were 100% in patients with alcohol chronic pancreatitis and 94.44% in the controls. The tests found no ADH2*3 allele in examined groups. ADH3*1 allele frequency was 68.18% and 40.74%, respectively. Genotype number and allele frequencies of ADH2 and ADH3 in the groups examined are presented in Tables I and II.

ADH2*1 and ADH3*1 alleles were statistically more frequent among the patients with ACP in comparison to the controls ($p<0.05$ and $p<0.001$, respectively). In the group of patients who abused alcohol, the differences were not statistically significant ($p>0.05$). The ADH2*2 allele was not detected in ACP patients.

In the population examined, the ADH2*1/*1 genotype was determined in 134 individuals, and the ADH2*1/*2 genotype was detected in 7 patients. The ADH2*2/*2 genotype was not found at all.

In no patient with ACP was the ADH2*1/*2 genotype presented. All were ADH2*1/*1 homozygotic. The ADH2*1/*1 and ADH3*1/*1 genotypes were statistically more frequent among the patients with alcohol pancreatitis than among the controls ($p<0.05$ and $p<0.001$, respectively), but the difference was not statistically significant between the ACP group and alcoholics ($p>0.05$). Comparison of ADH3*2/*2 genotype frequency in the studied groups showed that it was statistically significantly rarer among patients with ACP than among alcoholics and controls.

In the study group, only the ALDH2*1 allele was detected, all patients were ALDH2*1/*1 homozygotic.

In the examined population, all of which abused alcohol, the c2 allele frequency was 0.71% (Table III). In the group of patients with ACP, it was 2.27%. The c2/c2 genotype was not found in any patient. The genotype c1/c1 occurred in 139 patients, and heterozygotes c1/c2 were present in only 2 patients (with ACP). The c1/c2 genotype was not demonstrated in alcoholics. Differences in the allele and genotype distribution in the examined groups were not significant.

Discussion

Genetic polymorphism of the enzymes involved in alcohol metabolism is relevant in the etiopathogenesis of ACP. It is highly ethnically and race dependent. The ADH2*2 allele is decisively more common among Asians (60% to 80%) than among the white population (0% to 10%) [22]. The ADH2*2 allele is 1.3–2 times more frequent among the non-drinkers than among patients who abuse alcohol [23–25].

Table I. Genotype number and allele frequencies (%) of ADH2 in the groups examined.

Patient group	*n*	Genotype			Allele	
		*1/*1	*1/*2	*2/*2	*1	*2
Chronic alcohol pancreatitis	44	44* NS	0* NS	0	100* NS	0* NS
Healthy alcoholics	43	42	1	0	98.84	1.16
Control	54	48	6	0	94.44	5.56
Total	141	134	7	0	97.52	2.48

*$p<0.05$ versus control group.
NSNon-significant difference versus healthy alcoholics.

Table II. Genotype number and allele frequencies (%) of ADH3 in the groups examined.

		Genotype			Allele	
Patient group	*n*	*1/*1	*1/*2	*2/*2	*1	*2
Chronic alcohol pancreatitis	44	17* NS	26# NS	1* **	68.18* NS	31.82* NS
Healthy alcoholics	43	17	17	9	59.30	40.70
Control	54	10	24	20	40.74	59.26
Total	141	44	67	30	54.96	45.04

*$p < 0.001$ versus control.
**$p < 0.001$ versus healthy alcoholics.
NSNon-significant difference versus healthy alcoholics.
#NSNon-significant difference versus healthy alcoholics and versus control.

In our study, ADH2*1 alleles occurred statistically significantly more frequently among the ACP patients than among the controls, but the differences between the groups of patients who abused alcohol were not statistically significant. So, they favor developing alcohol consumption but not necessarily developing ACP. On the other hand, ADH2*2 alleles predominated among non-drinkers. The ADH2*2 allele may thus be a protector against alcoholism only. In other studies, however, the role for the ADH2 polymorphism has been found in ACP [26,27].

The role of alcohol-metabolizing enzyme gene polymorphisms is controversial and not clear. There are a few reports in the literature discussing the relationship between ACP and ADH3 genetic polymorphism. Chronic alcohol pancreatitis was more common in ADH3*1 and ADH3*2 homozygotes than heterozygotes. Heterozygotic alleles seem to be protective in the etiology of chronic pancreatitis [28]. Our results were different. In the group with ACP the most common was the heterozygotic ADH3*1/*2 genotype; however, 2.3% were homozygotic ADH3*2/*2 genotype. Thus, presence of the ADH1C*2/*2 genotype generally does not favor alcoholism and may protect against ACP. On the other hand, ADH3*1 alleles were markedly concomitant with chronic pancreatitis of alcoholic etiology and healthy alcoholics. Day et al. [8] and Dumas et al. [29] suggested a relationship between the ADH3*1 allele and ACP, although there are studies of Caucasian and Japanese populations in which no relationship was found between ADH3 polymorphism and pancreatitis [27,30–33].

Frequency of the ALDH2 alleles varies among populations. The ALDH2*2 allele occurs mainly in oriental populations, i.e. Japanese, Chinese, inhabitants of Taiwan and Korea, and protects against developing alcoholism and alcohol liver disease [20,34–37]. Its role in alcohol pancreatitis was not evaluated. Investigations of the Caucasian race have found an almost totally homozygotic character of ALDH2*1 [9,22,38]. Our observation here is similar. No variations in ALDH alleles or genotypes were found. In the studied group, none of the patients examined presented the ALDH2*2 allele. All were homozygotic ALDH2*1/*1, so we could not examine correlations between ALDH2 gene polymorphism and ACP.

The role of genetic polymorphism of CYP2E1 in ACP is poorly defined and remains unclear. In our study, the c2 allele frequency was 2.27% of patients with ACP. In the group of Italian patients with ACP its prevalence was 2.3% [39], as in our study. Such a rare presence of this allele in the above-mentioned group of patients did not allow us to draw explicit conclusions. We did not found relations between this disease and CYP2E1 polymorphism. Similarly, results published by other authors do not support the hypothesis of correlation between the c2 allele and ACP [26,27]. Yang et al. [40] and Verlaan et al. [41] studying the Caucasian population did not demonstrate statistically significant differences in the presence of the c2 allele among patients with ACP, idiopathic pancreatitis, healthy alcoholics and controls.

Studies concerning the role of the glutathione S-transferase gene in development of ACP show that the GSTM1 null genotype seems to protect a subset

Table III. Genotype number and allele frequencies (%) of CYP2E1 in the groups examined.

		Genotype			Allele	
Patient group	*n*	c1/c1	c1/c2	c2/c2	c1	c2
Chronic alcohol pancreatitis	44	42	2	0	97.73	2.27
Healthy alcoholics	43	43	0	0	100	0
Control	54	54	0	0	100	0
Total	141	139	2	0	99.29	0.71

Differences in genotype number and allele frequencies between the groups defined were not significant.

of subjects (women under age of 50 years) from this disease [42].

In conclusion, our analysis and studies presented suggest that the ADH3*1 and ADH2*1 alleles may be risk factors for developing alcoholism. The ADH3*2/*2 genotype may confer protection against ACP. CYP2E1 gene polymorphism is not related to alcoholism and ACP. The Polish population examined is ALDH2*1/*1 homozygotic.

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