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Analysis of clinical course of chronic pancreatitis in children with IVS8-5T variant in comparison with patients with *CFTR* mutation-related pancreatitis

Analiza przebiegu przewlekłego zapalenia trzustki u dzieci z wariantem IVS8-5T w porównaniu z pacjentami z przewlekłym zapaleniem trzustki związanym z mutacjami w genie *CFTR*

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Keywords

chronic pancreatitis, children, polymorphism, *CFTR* mutation, clinical course

Słowa kluczowe

przewlekłe zapalenie trzustki, dzieci, polimorfizm, mutacje genu *CFTR*, przebieg kliniczny

Summary

Introduction. Chronic pancreatitis (CP) in children is a rare entity with varied etiological factors. Gene mutations are proven to be related with pancreatitis and account for the most common cause of CP in children. One of the most frequently described genetic variant is the 5T polymorphism in intron 8 (IVS8-5T) of *CFTR* gene. Its contribution to development pancreatitis remains unclear and is still investigated. Data about 5T variant in etiology of children CP are very limited.

Aim. The aim of the study was to analyze the clinical course of CP in children with the 5T variant in comparison with CP children with *CFTR* mutations.

Material and methods. The 277 children with CP hospitalized in the Department of Gastroenterology of The Children's Memorial Health Institute between 1988 and 2015 were enrolled into the study. As the only potential genetic factor causing CP, the 5T variant was found in 15 children (group 1) and *CFTR* mutation in 10 children (group 2). Medical charts of patients were reviewed, clinical data was compared between groups.

Results. We found no statistically significant differences in the age of diagnosis (1.58-17.27 vs. 3.48-16.81 years; NS), number of pancreatitis episodes (1.0-6.0 vs. 1.0-9.0; NS), nutrition status (Cole's ratio mean 93.7 vs. 100.9%; NS), number of calcifications on imaging (4 vs. 3; NS), frequency of pancreatic duct stenting (4 vs. 4; NS), surgical interventions (6 vs. 1; NS) or endocrine (2 vs. 0; NS) and exocrine insufficiency (1 vs. 1; NS).

Conclusions. The clinical course of CP in children with the 5T variant and children with *CFTR* mutation is comparable.

Konflikt interesów
Conflict of interest

Brak konfliktu interesów
None

Streszczenie

Wstęp. Przewlekłe zapalenie trzustki (PZT) jest chorobą o zróżnicowanej etiologii, rzadko występującą u dzieci. Udowodniono, że mutacje w genach *SPINK1*, *CFTR*, *PRSS1*, *CTRC* i *CPA1* mają związek z etiologią PZT i są to najczęstsze czynniki etiologiczne u dzieci. Jednym z najczęściej opisywanych wariantów genetycznych jest polimorfizm w intronie 8 (IVS8-5T) w genie *CFTR*. Istnieją dane potwierdzające związek polimorfizmu IVS8-5T z etiologią PZT, lecz zagadnienie pozostaje nierozstrzygnięte. Informacje o roli wariantu w PZT u dzieci są bardzo ograniczone.

Cel pracy. Celem pracy była analiza przebiegu klinicznego PZT u dzieci z wariantem 5T w porównaniu z PZT związanym z mutacją w genie *CFTR*.

Materiał i metody. Do badania włączono 277 dzieci w PZT hospitalizowanych w Klinice Gastroenterologii, Hepatologii, Zaburzeń Odżywiania i Pediatrii w latach 1988-2015. Wariant 5T jako jedyną zmianę genetyczną związaną z PZT wykryto u 15 dzieci (grupa 1), mutację w genie *CFTR* u 10 dzieci (grupa 2). Przeanalizowano historie choroby pacjentów oraz porównano dane kliniczne.

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Wyniki. Nie odnaleziono istotnych statystycznie różnic w zakresie wieku rozpoznania choroby (1,58-17,27 vs. 3,48-16,81 roku; NS), liczby zaostrzeń PZT (1,0-6,0 vs. 1,0-9,0; NS), stanu odżywienia (średnia wskaźnika Cole'a 93,7 vs. 100,9%; NS), liczby zwapnień uwidocznionych w badaniach obrazowych (4 vs. 3; NS), częstości stentowania przewodu trzustkowego (4 vs. 4; NS), operacji (6 vs. 1; NS) czy niewydolności wewnątrz- (2 vs. 0; NS) i zewnątrzwydzielniczej (1 vs. 1; NS).

Wnioski. Przebieg kliniczny PZT u dzieci z wariantem 5T oraz u dzieci z mutacją w genie *CFTR* jest porównywalny.

INTRODUCTION

Chronic pancreatitis (CP) is a rare entity in children, but with increasing prevalence all over the world. Causes of CP in pediatric patients differ significantly from those described in adults, and the most frequent are gene mutations, anatomical defects, biliary tract diseases or lipid disorders. The most important genes which mutations are associated with pancreatitis include: *PRSS1* (cationic trypsinogen/serine protease 1) (1), *SPINK1* (serine protease inhibitor, Kazal type 1) (2), *CFTR* (cystic fibrosis transmembrane conductance regulator) (3), *CTRC* (chymotrypsin C) (4) and *CPA1* (carboxypeptidase A1) (5). Mutation in the *PRSS1* gene is a confirmed cause of chronic pancreatitis (6-8) in contrast to other genes, which mutations only increase the risk of the disease (7, 9). Despite the dynamic development of imaging techniques and genetic testing, a great number of pancreatitis still remains idiopathic.

Mutations of *CFTR* gene cause cystic fibrosis (CF), an autosomal recessive condition caused by loss-of-function mutations of gene encoding *CFTR* protein, ion channel at the plasma membrane (10). From over 2006 known so far *CFTR* mutations (according to *CFTR* Mutation Database) (11). The p.Phe508del mutation accounts for approximately 56-70% of CF-causing alleles in Caucasian population (12). Cystic fibrosis disease phenotype is quite variable (from severe pulmonary disease with pancreatic insufficiency to severe pulmonary disease with pancreatic sufficiency or atypical CF), and other conditions are also associated with *CFTR* gene mutation (e.g. congenital bilateral absence of vas deferens or disseminated bronchiectasis). In 1998 Cohn et al. (3) proved a strong association between *CFTR* mutation and idiopathic pancreatitis. As mentioned above, many *CFTR* mutations has been described, and therefore a classification system has been established to simplify the genotype/phenotype correlation. Due to pancreatic function status Kristidis et al. classified mutations as severe (pancreatic insufficiency – PI) or mild (pancreatic sufficiency – PS) (13). Other classification divides mutations in classes – class I, II, III result in total loss of *CFTR* function, class IV or V mutations have some residual ion channel function (14). Except for mutations, clinicaly significant polymorphisms in *CFTR* gene have also been described (15). In polymorphic Tn locus in intron 8 of *CFTR* three different numbers of thymidine repeats can be found – T5, T7 or T9 (16).

Variant 8 consisting of a short polythymidine tract (5T instead of 7T or 9T) determines the efficiency by which the intron 8 splice acceptor is used what results in a high proportions of transcript without exon 9. The efficiency of splicing decreases together with decreasing number of T repeats (17). Furtheremore, the effect of 5T variant is modulated by another polymorphic tract in intron 8 – TG(n). This track typically consist of 11, 12 or 13 TG repeats. The IVS8-5T *CFTR* variant when accompanied with 12 or 13 TG repeats on the same allele give rise to less efficient splicing (17). A IVS8-5T(TG)12 or IVS8-5T(TG)13 *CFTR* gene found in compound heterozygosity with a CF-causing mutation, or possibly even in homozygosity, will in general result in a *CFTR*-related disorder, such as CBAVD or CP (14). On the contrary, IVS8-5T(TG)11 in such situation can lead to *CFTR*-related disorder or do not have any clinical relevance.

Polymorphic 5T variant was found to be connected with idiopathic chronic pancreatitis in several studies (18, 19). Furthermore, in a subgroup of patients it was found to be a single genetic alteration identified, but its contribution to the etiology of CP remains controversial.

AIM

Thus, the aim of the study was to analyze and compare the clinical course of CP between children with 5T variant and *CFTR* mutations.

MATERIAL AND METHODS

Total of 277 children with CP hospitalized at the Department of Gastroenterology, The Children's Memorial Health Institute, Warsaw, Poland, between 1988 and 2015 were enrolled in the study. The inclusion criteria were: age 18 years, diagnosis of CP verified by imaging methods (US scan, CT, magnetic resonance cholangiopancreatography [MRCP], and/or endoscopic retrograde cholangiopancreatography [ERCP]), and follow-up of 12 months from time of the first visit.

260 (94%) participants were screened for mutations in the high-risk genes associated with CP. Written consents from patients and their parents were obtained before the analysis. *CFTR* (cystic fibrosis transmembrane conductance regulator); OMIM (Online Mendelian Inheritance in Man) 602421; was screened for p.Phe508del (p.Phe508del), dele2,3(21kb) mutations and variant IVS8-5T. In some of patients direct Sanger sequencing of exons 9-11 was performed, which enabled additionally exclude rare *CFTR* mutations locat-

ed in this regions). Molecular analysis was performed at the Department of Medical Genetics of Institute of Mother and Child, Warsaw, Poland (between 1988-2010, and 2012-15), Genomed S.A., Warsaw, Poland (2011-2012), or Medgen, Warsaw, Poland (2012).

All patients underwent imaging studies, including abdominal ultrasound, CT, MRCP and/or ERCP. Clinical data were recorded and analyzed. Family history, laboratory and genetic results, the results of imaging studies, surgical and endoscopic procedures were documented.

The clinical course of CP was investigated on the basis of following parameters: 1) age of the disease onset regarded as first documented episode of acute pancreatitis (acute pancreatitis was diagnosed on the basis of elevated activity of serum amylase more than triple excess over the upper normal range [reference value: 0-82 U/L], elevated urine amylase activity [reference value: 0-380 U/L], and/or serum lipase activity 5 times over the upper normal range [reference value 0-210 U/L]), 2) number of pancreatitis episodes, 3) nutrition status (BMI = actual weight [kg]/height [m^2]; Cole's ratio = (BMI actual/BMI for the 50th centile) x 100 [%]), 4) changes found on imaging studies (US scan and/or MRCP), 5) the frequency of pancreatic duct stenting, 6) frequency of surgical procedures, 7) endocrine sufficiency and 8) exocrine sufficiency based on pancreatic function tests (the 72-h fecal fat quantification, elastase-1 stool test, breath test with 13C-mixed substrates estimating exocrine pancreatic function).

Patients were divided into 2 subgroups depending on *CFTR* genetic alteration: group 1 – children with the 5T variant, group 2 – children with *CFTR* mutation. Patients with any other etiological factor accompanying investigated *CFTR* alterations were excluded.

Data were reported as mean standard deviation or as median and range for continuous variables, and as relative frequencies for categorical variables. The chi-square test was used to compare relative frequencies. Analysis of continuous variables was performed using the Mann-Whitney U test and Kruskal-Wallis test (Statistica for Windows, v5.0; StatSoft, Tulsa, OK, USA). Significance was assumed at $P < 0.05$.

RESULTS

The 5T variant was found in 26 (10%) and *CFTR* mutation in 20 patients (7.6%) out of 260 cases. After exclusion of children with any other genetic alteration associated with CP detected there were 15 children with the 5T variant and 10 children with *CFTR* mutation (9 children with p.Phe508del/-, 1 child with dele2,3(21kb)). Number of TG repeats was established in 5 patients and in all cases it was IVS8-5T(TG)11. The rest of children had their genetic testing done before implementing the analysis of number of TG repeats into routine diagnostic schedule, which was in 2008 (14). Some patients had diagnosed some other risk factors of pancreatitis, as shown in table 1.

Tab. 1. Genetic characteristics of patients

Patients	Sex	IVS8-	TG repeats in cis with IVS8-5T	*CFTR*	Other risk factor
1.	M	5T/9T	Not tested	–	–
2.	M	5T/7T	Not tested	–	–
3.	F	5T/9T	Not tested	–	Cholelithiasis
4.	M	5T/9T	Not tested	–	–
5.	M	5T/9T	Not tested	–	Choledochal cyst and APBU
6.	F	5T/9T	Not tested	–	–
7.	M	5T/7T	TG(11)	–	–
8.	M	5T/9T	Not tested	–	–
9.	F	5T/9T	Not tested	–	Pancreas divisum
10.	F	5T/7T	TG(11)	–	Ansa pancreatica
11.	F	5T/7T	TG(11)	–	–
12.	F	5T/7T	TG(11)	–	–
13.	M	5T/7T	Not tested	–	–
14.	F	5T/7T	TG(11)	–	–
15.	F	5T/7T	Not tested	–	–
16.	F	–	–	Phe-508del/-	–
17.	M	–	–	Phe-508del/-	–
18.	M	–	–	Phe-508del/-	–
19.	M	–	–	Dele-2,3(21kb)/-	–
20.	F	–	–	Phe-508del/-	–
21.	F	–	–	Phe-508del/-	Hypertriglyceridemia
22.	F	–	–	Phe-508del/-	Pancreas divisum
23.	F	–	–	Phe-508del/-	–
24.	M	–	–	Phe-508del/-	Hypertriglyceridemia
25.	F	–	–	Phe-508del/-	–

Family history was positive in 5 children (33.3%) from group 1 and in 3 children (30%) from group 2. The mean age of onset of chronic pancreatitis in group 1 was 7.9 years vs. 9.9 in group 2 (NS). Nutrition status evaluated on the basis of Body Mass Index (BMI mean 16.33 vs. 18.59; NS) and Cole's ratio (mean 93.66 vs. 100.87%; NS) did not differ significantly. There was no statistical significance in difference of number of pancreatitis episodes between investigated groups (1.0-6.0

vs. 1.0-9.0; NS), number of calcifications on imaging studies (4.0 vs. 3.0; NS), pancreatic duct stenting (4.0 vs. 4.0; NS), surgeries (6.0 vs. 1.0; NS), endocrine or exocrine insufficiency (2.0 vs. 0.0; NS, 1.0 vs. 1.0; NS).

General characteristics of patients in investigated groups shown in table 2.

Tab. 2. Comparison of clinical characteristics of children with the 5T variant and *CFTR* mutation

Characteristic	Group 1 (IVS8-5T variant) N = 15	Group 2 (*CFTR* mutation) N = 10	P value
Age of disease onset (yr) Range Mean	 1.58-17.27 7.9	 3.48-16.81 9.9	NS
Number of episodes Range Mean	 1.0-6.0 4.6	 1.0-9.0 3.1	NS
Nutrition status BMI (range) mean Cole's ratio (range) (%) mean	 14.11-18.73 16.33 80.68-107.31 93.66	 13.22-22.06 18.59 84.75-122.07 100.87	NS
Calcifications; n (%)	4 (26.7)	3 (30)	NS
Pancreatic duct stenting; n (%)	4 (26.7)	4 (40)	NS
Surgery; n (%)	6 (40)	1 (10)	NS
Diabetes; n (%)	2 (13,3)	0 (0)	NS
Exocrine insufficiency; n (%)	1 (6,7)	1 (10)	NS

NS – not significant

DISCUSSION

Frequency of the 5T variant in general population is about 10% (5% for allele population) (20) which is the same as in our cohort (26/260 patients). Comprehensive testing of genetic alteration in French group of adult patients with ICP detected the 5T variant frequency of 9.7%, which was nearly two times greater than control group frequency, but still statistically insignificant as well (p = 0.093) (19). Moreover, in literature there are some other data contrasting with our results – in research conducted by Bishop et al. (21), the 5T variant was found in 16% of the pancreatitis adult patients, which exceeds the frequency observed in control group or 13% pancreatitis alleles vs. 5% of general allele population reported by Noone et al. (22).

Association of CP with *CFTR* mutation is well documented (3,23), and the prevalence of mutations in the *CFTR* gene in patients with idiopathic chronic pancreatitis ranges from 13 to 37% (24). However, in our cohort incidence of *CFTR* mutation was 7.6% (20/260). Contrasting data come from group of 29 children with CP or ARP with an average age on the onset of disease of 5 years old, described by Sultan et al. *CFTR* gene mutations turned out to be most frequently described mutations in the cohort with prevalence of 48% (25).

The natural history of *CFTR* alteration-associated pancreatitis is not well known and the literature data concerning pediatric population is extremely limited. The studies mentioned below are from adult population and hence head-to head comparisons to pediatric population cannot be made.

Study conducted in United Kingdom on 134 patients with CP made an assessment of some clinical data in patients with the 5T variant and *CFTR* mutation (18). The 5T variant was found in 10.4% patients of all cohort, but after excluding patients with *CFTR* mutation, there were 7.4% patients with the 5T variant alone. Similarly *CFTR* mutation was described in 13.4% of all group, but as the only detected etiological factor of CP in 10.4%. There was no difference in the age of onset of the disease between patients (26 vs. 26yr). Pancreatic calculi was present in 40% of patients with the 5T variant and in 64% of patients with *CFTR* mutation. Exocrine insufficiency was diagnosed slightly more often in patients with *CFTR* mutation (10 vs. 43% respectively), similarly the drug-controlled diabetes and insulin-dependent diabetes was more frequently present in patients with mutation of *CFTR* gene (0 vs. 14% and 10 vs. 29% respectively), however, statistical significance for these data was not established.

French study of Pelletier et al. (26) aimed to describe natural history of *CFTR*-related chronic pancreatitis in adults. It compared the clinical data between group with common *CFTR* mutations (n = 12 patients, 9 with p.Phe508del mutation) and group with uncommon *CFTR* mutation (n = 23, 20 with the 5T variant). Commented research also failed to find differences in clinical course according to genetic alteration, no characteristic reached the statistical significance (exocrine insufficiency in patients with *CFTR* common mutation vs. *CFTR* uncommon mutation: 0 vs. 4; diabetes mellitus 1 vs. 2; calcification/ductal lesions 6 vs. 16; endoscopic/surgical treatment 4 vs. 6).

Hamoir et al. (27) investigated a cohort of 351 adult patients with CP due to correlate the clinical features of the disease with the genetic cause. The study group consisted of 61 patients with at least one mutation described, and the *CFTR* mutations appeared to be the most common one, diagnosed in 34 patients (9.7% of all cohort). Polymorphisms including IVS8-5T were excluded. The clinical data were compared to control group without any etiological factor of CP known. The clinical course was evaluated on the basis of mean age of the disease onset (36 vs. 29yr; NS), mean number of hospitalization (3 vs. 3; NS), exocrine and endocrine insufficiency (26.5 vs. 26.2%; NS and 14.7 vs. 16.4%; NS respectively), calcifications (35.3 vs. 42.7%; NS). The clinical course of *CFTR* mutation-related CP did not differ from the ICP. Authors also investigated frequency of endoscopic and surgical treatment and again there were no statistically significant differences between compared groups (38.2 vs. 49.2%; NS and 11.7 vs. 14.7%; NS respectively). Interesting finding of authors was higher risk of pancreatic cancer (PC) in patients with *CFTR* mutations in comparison with ICP and even with *PRSS1* related CP. But in pediatric population PC is extremely rare condition. As the role of the 5T variant in CP etiology is still unproven, our group

of patients with the 5T variant could be compared to ICP patients. Assuming that, our results of comparing the clinical course stay in compliance with results of Hamoir et al.

Interesting data concerning the clinical course of CP related to alteration of *CFTR* gene can be found in the study of 78 adult patients with ICP from Taiwan (28). However, it needs to be emphasized, that mutations in *CFTR* gene differs worldwide, and other than the most common European mutations were detected in Taiwanese cohort. The 5T variant was found in 7.6% of patients, at least one *CFTR* mutation in 24.4%. The 5T variant was associated with earlier age of ICP onset ($p = 0.009$, compared with patients with ICP without T5 mutation). The rest of characteristics evaluating the clinical course: number of episodes of CP (2 vs. 2; NS), number of calcification (4 vs. 11; NS), diabetes mellitus (3 vs. 7; NS), pseudocysts and pancreatic duct structures (0 vs. 2; NS) did not differ significantly, which corresponds with our findings.

CONCLUSIONS

The role of the 5T variant in the etiology of chronic pancreatitis remains controversial. We found no statistically significant differences in characteristics of clinical course of chronic pancreatitis between CP related to the IVS8-5T variant and *CFTR* mutation in our pediatric population. It appears to be no clear genotype-phenotype correlation within the CF mutation-associated chronic pancreatitis group, however, this may be because of too small patient groups were analyzed or because TG variant was not established in all of cases. More studies with larger sample size concerning the clinical course of chronic pancreatitis related to gene alterations in children are necessary to obtain more reliable data.

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