The clinical course of chronic pancreatitis associated with lipid disturbances in children

Przebieg kliniczny przewlekłego zapalenia trzustki związanego z zaburzeniami lipidowymi u dzieci

Grzegorz Oracz, Jarosław Kierkuś, Jerzy Socha, Józef Ryżko

Department of Gastroenterology, Hepatology and Immunology, The Children's Memorial Health Institute, Warsaw, Poland

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Address for correspondence: Grzegorz Oracz MD, PhD, Department of Gastroenterology, Hepatology and Immunology, The Children's Memorial Health Institute, 20 Al. Dzieci Polskich, 04-730 Warsaw, Poland, phone: +48 22 815 74 87, fax: +48 22 815 73 82, e-mail: agoracz@wp.pl

Abstract

Introduction: Chronic pancreatitis (CP) is a rare disease in childhood, characterized by continuous damage of the structure, function, or both, of the pancreas because of progressive inflammation. The etiology of CP in children varies and includes anatomic anomalies, gene mutations, metabolic disorders and others. The reported pediatric experience with chronic pancreatitis (CP) is small and little is known about the role of hyperlipidemia.

Aim: To evaluate the role of lipid disturbances as a cause of chronic pancreatitis in children.

Material and methods: One hundred and eighty children with CP, hospitalized from 1995 to 2010, were enrolled in the study. Medical records of these patients were reviewed for clinical presentation and diagnostic findings.

Results: Lipid disturbances were found in 25 patients (13.8%). Hypertriglyceridemia was detected in 15 patients, hypercholesterolemia in 14 patients. In 10 patients with CP and lipid disturbances other factors causing CP were present (gene mutations in 6 patients and anatomic anomalies in 6 patients). There was no statistically significant difference in the clinical course between the hyperlipidemic (HA group) and non-hyperlipidemic group (NHA group).

Conclusions: Chronic pancreatitis associated with lipid disturbances is common in children and has a similar clinical course as chronic pancreatitis without lipid disturbances. We should be aware of coexistence of hyperlipidemia and other factors causing pancreatitis, such as gene mutations.

Streszczenie

Wstęp: Przewlekłe zapalenie trzustki (PZT) jest rzadką chorobą u dzieci. Przewlekły proces zapalny powoduje postępujące i nieodwracalne włóknienie trzustki. Do najczęstszych przyczyn PZT u dzieci należą mutacje genów, wady anatomiczne przewodu trzustkowego, choroby dróg żółciowych oraz zaburzenia lipidowe. Wiedza na temat roli zaburzeń lipidowych w rozwoju i przebiegu klinicznym PZT jest niewielka.

Cel: Ocena wpływu zaburzeń lipidowych na ciężkość przebiegu klinicznego PZT u dzieci.

Materiał i metody: Do badania włączono 180 dzieci z PZT hospitalizowanych w latach 1995–2010 w Klinice Gastroenterologii Centrum Zdrowia Dziecka. Na podstawie danych z historii choroby u tych pacjentów odtworzono retrospektywnie przebieg kliniczny PZT.

Wyniki: Zaburzenia lipidowe stwierdzono u 25 chorych (13,8%). Hipertriglicerydemię rozpoznano u 15, a hipercholesterolemię u 14 dzieci. U 10 pacjentów odnotowano równocześnie inne czynniki predysponujące do PZT (mutacje genów u 6 i wadę anatomiczną przewodu trzustkowego u 6 dzieci). Nie stwierdzono znamiennej statystycznie różnicy w ciężkości przebiegu PZT u chorych z zaburzeniami lipidowymi w porównaniu z pozostałymi pacjentami.

Wnioski: Zaburzenia lipidowe są jednym z częstszych czynników etiologicznych PZT u dzieci. Przebieg kliniczny tego schorzenia związanego z zaburzeniami lipidowymi nie różni się od przebiegu PZT o innej etiologii. Należy pamiętać o stosunkowo częstym współwystępowaniu zaburzeń lipidowych z innymi czynnikami etiologicznymi, takimi jak mutacje genów predysponujących do zapalenia trzustki.

Introduction

Chronic pancreatitis (CP) is a rare disease in childhood, characterized by continuous damage of the structure, function, or both, of the pancreas because of progressive inflammation. Chronic pancreatitis is the result of repeated attacks of acute pancreatitis (AP). Once initiated, the disease follows a relentless course. Most adult patients have alcohol-induced CP. The prevalence of CP varies from 20 to 200 per 100 000 in the general population, and is increasing as a result of environmental factors [1, 2].

The pathogenesis of CP is poorly understood. The etiology of CP in children is varied and includes gene mutations, anatomic anomalies, metabolic disorders and others [1, 3, 4]. The reported pediatric experience with CP is small and little is known about the role of lipid disturbances. However, the literature on the subject is conflicting because most of the information is found within individual case reports or small case series [5-8]. Disorders in lipoprotein metabolism can result in pancreatitis. Very high triglycerides resulting from elevated chylomicrons are associated with increased risk of pancreatitis. The mechanism underlying this association is uncertain, but the relatively unique capacity of the pancreas to produce an exocrine lipase might play a role [9, 10]. Discrepancies exist over its clinical, biological, and prognostic features.

Aim

The aim of our study was to evaluate the role of lipid disturbances as a cause of chronic pancreatitis in children.

Material and methods

The Children's Memorial Health Institute in Warsaw as a leading national pancreatic centre admits most of the pediatric chronic pancreatitis cases from the whole of Poland. One hundred and eighty children with CP hospitalized between 1995 and 2010 in the Department of Gastroenterology were enrolled in the study. Most of the patients were admitted during a remission period, for clinical and genetic investigation and/or treatment.

The inclusion criteria were: age ≤ 18 years, diagnosis of CP verified by imaging methods (ultrasound (US) scan, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP)), and an observation period of ≥ 12 months from the first visit. Children with acute pancreatitis were excluded from the study. For patients under 15 years of age, factors predisposing to pancreatitis such as alcohol consumption and smoking were excluded.

Chronic pancreatitis was defined according to the Cambridge classification system [11]. Clinical data were recorded and analyzed. Family history, laboratory results, results of imaging methods (US scan, MRCP, ERCP), and surgical and endoscopic treatment were documented. The first episode of acute pancreatitis diagnosed on the basis of serum amylase activity ≥ 3 times over the upper normal range (reference value 0-82 U/l), elevated urine amylase activity (reference value: 0-380 U/l) and serum lipase activity ≥ 5 times over the upper normal range (0-210 U/l) was regarded as the onset of CP.

The behavior of the disease was established based on the following parameters: age of disease onset; number of pancreatitis episodes; changes found in the imaging methods (US scan and/or MRCP); changes in ERCP according to the Cambridge scale; results of the endocrine end exocrine pancreatic function tests (oral glucose tolerance test, elastase-1 in stool, 72-h fecal fat balance); endoscopic and surgical treatment.

All children were screened for gene mutations predisposing to CP: CFTR (cystic fibrosis transmembrane conductance regulator; OMIM 602421), PRSS1 (cationic trypsinogen/serine protease 1; OMIM 276000) and SPINK1 (serum protease inhibitor Kazal type 1; OMIM 167790).

The diagnosis of hereditary pancreatitis (HP) was made when a defining gene mutation in the PRSS1 gene was identified or when two first-degree relatives or three or more second-degree relatives, in two or more generations, suffered from recurrent acute pancreatitis and/or CP.

Endoscopic retrograde cholangiopancreatography was carried out as a standard procedure in patients presenting with evidence of pancreatic duct obstruction (in US scan or MRCP). Polyethylene stents were placed to optimize pancreatic drainage when necessary. All stents were placed at the discretion of the interventional endoscopist, based on pancreatogram findings.

Serum lipids were measured after 12-h fasting. Plasma total cholesterol and triglycerides were measured by enzymatic methods. Hyperlipidemia was defined according to the National Cholesterol Educational Program (ATP III) system [12].

Elastase-1 in the stool ELISA test (Schebo-Tech, Germany) was performed in all patients (reference value > 200 µg/g). The 72-h fecal fat balance (g/day) was evaluated by collecting stool samples pooled over a 3-day period (Kramer's and Weyer's method; reference value < 4.0 g/day). All children were examined for endocrine insufficiency (oral glucose tolerance test).

The patients and parents were informed of the aims of the project and they signed written agreement for clinical and molecular procedures to be used.

The Local Ethical Committee approved the study (53/KBE/2003).

Statistical analysis

Data were reported as mean ± standard deviation, or as median and range for continuous variables, and as relative frequencies for categorical variables. The χ^2 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). Significance was assumed at $p < 0.05$.

Results

Lipid disturbances were found in 25 patients (13.8%) (15 girls and 10 boys with mean age 10.2 years, range: 4.2-16.4 years). We detected hypertriglyceridemia in 15 patients (8.3%). Median triglyceride level was 773 mg/dl (range: 206-5214 mg/dl). Hypercholesterolemia was found in 14 children (7.8%). Median cholesterol level was 265 mg/dl (range: 222-482 mg/dl).

In 10 patients (5.6%) with CP and lipid disturbances other factors causing CP were present. In 6 patients (3.3%) we found gene mutations predisposing to CP (CFTR-deltaF508/– in 3 patients and SPINK1– in 3 patients [N34S/– in 2 patients and compound heterozygote N34S/IVS3+2T>c in 1 child]). Anatomic anomalies of the pancreatic duct were found in 6 patients (3.3%) (pancreas divisum in 4 patients and ansa pancreatica in 2 children).

Hereditary lipoprotein lipase deficiency (OMIM 246650) was found in 1 patient. Nine patients (36%) were obese (body mass index > 95 percentile). In 3 patients (12%) from this group non-alcoholic steatohepatitis (NASH) was observed.

There was no difference in age of the disease onset between the hyperlipidemic (HA group) and non-hyperlipidemic group (NHA group) (10.2 years vs. 8.8 years, NS).

In all children with hyperlipidemia ERCP showed evidence of CP (1.6° Cambridge grade vs. 1.7° in the NHA group, NS). There was no difference in therapeutic intervention, including both surgical and endoscopic intervention (40% vs. 42.5% in the NHA group; NS). Pancreatic duct stenting was performed in 9 children in the HA group (36% vs. 34% in the NHA group; NS). One patient had extracorporeal shock-wave lithotripsy (ESWL) followed by ERCP (4% vs. 6% in the NHA group; NS).

There was no difference in pancreatic calcifications (40% vs. 38% in NHA group; NS). There was no correlation between triglycerides or cholesterol level and severity of CP. Diabetes mellitus was present in 3 children (12% vs. 8% in the NHA group; NS). Pancreatic insufficiency was observed less frequently in patients with hyperlipidemia (12% vs. 22% in the NHA group; $p < 0.05$).

Discussion

In recent years an increase in the number of children with CP has been observed in our hospital as well as in other pediatric centers worldwide [1, 3, 4, 13]. In contrast with adults, in whom alcohol and gallstones are the most common causes of CP, etiology in children is diverse [1, 3, 13]. The most common cases seen in our department resulted from gene mutations, anatomic anomalies of the pancreatic duct, biliary tract diseases and lipid disturbances [4].

Hyperlipidemia has been documented as a cause of pancreatitis in children. To date, there are a few case reports on the role of lipid disturbances in etiology of chronic pancreatitis in children [5-8].

Disorders in lipoprotein metabolism can result in pancreatitis. Lipid disturbances can be classified as hypercholesterolemia, hypertriglyceridemia, combined hyperlipidemia and low levels of high-density lipoprotein (HDL) cholesterol. All of the dyslipidemias can be primary or secondary. In the appraisal of the dyslipidemias, measurement of serum cholesterol, triglycerides, HDL and low-density lipoprotein (LDL) cholesterol is usually sufficient [9, 12]. In 2001, the National Cholesterol Educational Program (ATP III) identified optimum triglycerides as < 150 mg/ dl, borderline as 150-199 mg/dl, and high as 200-499 mg/dl. Triglyceride concentrations ≥ 500 mg/dl were classified as very high [12]. Triglyceride levels greater than 500 mg/dl significantly increase the risk for pancreatitis [2, 5, 9, 10, 14]. Hypertriglyceridemia-induced pancreatitis is seen in patients with familial types I, IV, and V hyperlipidemia and in patients with secondary hypertriglyceridemia due to obesity, diabetes mellitus or drugs [5, 9, 10, 14]. About 30% of cases of type I hyperlipidemia, 30-40% of type V, and 15% of type IV may be associated with pancreatitis [14]. Associated clinical clues include eruptive xanthomata and lipemia retinalis [9]. Pancreatitis secondary to hypertriglyceridemia presents typically as an episode of acute pancreatitis (AP) or acute recurrent pancreatitis (ARP), rarely as chronic pancreatitis. Interestingly, serum pancreatic enzymes may be normal or minimally elevated during acute episodes of pancreatitis, diagnosed by imaging studies [5, 10]. Because patients with acute pancreatitis tend to have raised triglyceride levels, the lipid levels have to be remeasured after the acute episode [1].

The frequency of hypertriglyceridemia in patients with acute pancreatitis ranges from 1.3% to 53% [5, 10, 14-16]. In patients with CP it is unknown. In our pediatric study the frequency of lipid disturbances was similar to that observed in adults with acute recurrent pancreati-

tis. Over 8% of patients with CP had hypertriglyceridemia, and 7.8% had hypercholesterolemia. According to the ATP III system, the mean triglyceride level in our patients was classified as very high.

The pathogenesis of pancreatitis associated with hypertriglyceridemia is not clear. The elevation in serum triglycerides probably induces the release of free fatty acids, responsible for the pancreatic damage. Hydrolysis of triglycerides in and around the pancreas by pancreatic lipase seeping out of the acinar cells leads to accumulation of free fatty acids in very high concentrations. Activated enzymes and oxygen free radicals are toxic and destroy acinar cells and capillary endothelium. This causes release of cytokines and vasoactive mediators, attraction of inflammatory cells and activation of vascular endothelium, as well as the expression of adhesion molecules. The disturbance of the pancreatic microcirculation could induce progression from edematous to necrotizing pancreatitis independent of early intracellular events, including protease activation [9, 10]. In animal models, infusion of high amounts of triglycerides causes pancreatitis-like changes and a rise of free fatty acids in the serum. As a consequence, the formation of microthrombi is enhanced and this may aggravate the disease by causing ischemic injury to the pancreas tissue [9].

The role of lipid disturbances as an etiological factor of CP is still controversial. It is not clear whether hyperlipemia represents an etiological factor or whether it is a risk factor, or possibly a combination of both. We analyzed 180 patients with CP with the major objective of understanding the causative role of hyperlipidemia in the disease pathology. Similarly to Fortson's study, in our group the clinical course of CP associated with hyperlipidemia is not different from that of pancreatitis of other causes [17]. There was no difference in age of disease onset, clinical presentation, and therapeutic intervention.

In our study, 10 patients with lipid disturbances (5.6%) had other potential factors that can induce CP (gene mutations and/or anatomic anomalies of the pancreatic duct). In the literature, patients with isolated hyperlipidemia without a predisposing factor rarely present with pancreatitis [5, 10]. Mutations in CFTR and SPINK1 genes have been described in patients with hypertriglyceridemia who develop pancreatitis [2]. Presence of the gene mutations and congenital anomaly confirms that pathogenesis of CP is still unclear and needs further studies. We should be aware of coexisting lipid disturbances and other factors, such as gene mutations, predisposing to chronic pancreatitis. Therefore, in the presence of one factor, the presence of a second one should be investigated.

The treatment of hypertriglyceridemia-induced pancreatitis is similar to that for other causes of pancreatitis. Therapy of chronic pancreatitis is usually limited to management of complications. It was reported that low-fat diets that decrease serum triglycerides might effectively prevent further episodes of pancreatitis [18]. In patients with severe hypertriglyceridemia (triglyceride level > 1000 mg/dl), reducing triglyceride levels may be necessary. Therefore therapeutic plasma exchange (TPE) has been used as emergent therapy to reduce the risk of pancreatitis [19].

Conclusions

Chronic pancreatitis associated with lipid disturbances is common in children and has a similar clinical course as CP of other causes. This study underscores the value of screening lipid levels in any patient who presents with pancreatitis. Observational studies are less powerful than clinical trials. Nonetheless, studies such as this initiative show that useful clinical information can be gained by observational data.

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