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Multifactorial cause of chronic pancreatitis in 14.5-year-old boy – a case report

Wieloczynnikowa przyczyna przewlekłego zapalenia trzustki u 14,5-letniego chłopca – opis przypadku

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Summary

Chronic pancreatitis (CP) is a rare disease in children, which is a recurring inflammatory process that leads to irreversible morphological changes in the pancreas, resulting in endocrine and exocrine insufficiency. The prevalence of CP in children is unknown. The pathogenesis of the disease is multifactorial. The most common causes of pancreatitis in children are gene mutations (*PRSS1*, *CFTR*, *SPINK1*, *CTRC*). Other important etiological factors of CP include anatomical defects of the pancreatic duct, biliary tract diseases, lipid disturbance and autoimmune diseases. In some cases more than one cause can be found. In this article we present a case of a 14.5-year-old patient with suspicion of chronic pancreatitis. Initially, abdominal trauma was suspected as the cause of pancreatitis. However, more than one cause of CP was discovered during the diagnostic course (gene mutations, pancreas divisum, ductal stone). It is difficult to determine which one was responsible for the development of the disease.

Streszczenie

Przewlekłe zapalenie trzustki (PZT) jest rzadką chorobą u dzieci, choć w ostatnich latach obserwuje się zwiększenie liczby chorych z PZT. Jest to nawracający proces zapalny, który prowadzi do nieodwracalnych zmian morfologicznych trzustki, co w efekcie powoduje niewydolność wewnątrz- i zewnątrzwydzielniczą. Patogeneza choroby jest wieloczynnikowa – najczęściej u jej podłoża leżą mutacje genów (*PRSS1*, *CFTR*, *SPINK1*, *CTRC*). Ważnymi czynnikami etiologicznymi PZT są również: wady anatomiczne przewodu trzustkowego, choroby dróg żółciowych, zaburzenia lipidowe czy choroby autoimmunologiczne. U dużego odsetka pacjentów nie udaje się ustalić przyczyny zapalenia trzustki, mówi się wówczas o „idiopatycznym" PZT. U części pacjentów występuje więcej niż jeden czynnik etiologiczny PZT. W artykule przedstawiono przypadek 14,5-letniego chłopca z podejrzeniem przewlekłego zapalenia trzustki. Początkowo podejrzewano u niego uraz jamy brzusznej jako przyczynę zapaleń trzustki, jednak w trakcie diagnostyki znaleziono więcej niż jedną przyczynę PZT. Chłopiec jest nosicielem mutacji w genach *SPINK1*, *CPA1*, *CFTR*. Badania obrazowe ukazały u niego kamicę przewodową oraz trzustkę dwudzielną. Trudno ustalić, która z tych przyczyn była odpowiedzialna za rozwój choroby.

Conflict of interest
Konflikt interesów
None
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INTRODUCTION

Chronic pancreatitis (CP) is a rare disease in children. Morbidity in the Polish pediatric population is about 20 cases per year. This disease is associated with periods of exacerbation and remission. It leads to irreversible pancreatic gland destruction with fibrosis which can result in impaired exocrine and endocrine dysfunction. The pathogenesis of this disease is multifactorial. The main causes include genetic mutations in *PRSS1* (cationic trypsinogen/serine protease 1), *CFTR* (cystic fibrosis transmembrane conductance regulator), *SPINK1* (serine protease inhibitor, Kazal type 1) and *CTRC* (chymotrypsin C) genes, anatomic anomalies, biliary tract diseases, metabolic disorders. In some patients there are more than one etiological factor. The clinical presentation is usually non-specific, especially in the early stages of the disease. The main symptom is strong abdominal pain, which may be

accompanied by vomiting, fever, jaundice, sometimes also bowel obstruction or shock. Often, abdominal pain is the only symptom. The discomfort is aggravated by eating, so patients often refuse food, which leads to weight loss and cachexia. Frequent exacerbations lead to exocrine insufficiency manifesting fatty diarrhea and intestinal absorption disorders.

Diagnosis of CP is based on studies of pancreas structure and function. Imaging studies such as ultrasound, computer tomography (CT scans), magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP) are most reliable in diagnosing CP. ERCP provides the most accurate visualization of the pancreatic ductal system and has been regarded as the criterion standard for diagnosing chronic pancreatitis. Laboratory tests are only a supplement to diagnostic approach. In the remission periods the activity of amylase and lipase is normal. Molecular studies on the mutation of genes predisposing to pancreatitis (*CFTR*, *PRSS1*, *SPINK1*, *CTRC*, *CPA1*) are also useful, especially in patients with suspicion of familial pancreatitis.

Chronic pancreatitis is an irreversible process. Treatment consists of nutrition education – high energy and protein diet. In addition, supplement pancreatic enzymes, fat soluble vitamins and trace elements should be provided. Whenever exacerbations are very frequent and pain is present, partial, subtotal or complete pancreas resection is performed. CP significantly increases the risk of developing pancreatic cancer (1).

CASE REPORT

14.5-year-old boy with suspicion of chronic pancreatitis was admitted to the Department of Gastroenterology, Hepatology, Feeding Disorders and Pediatrics, The Children's Memorial Health Institute for further investigation. Previously, he was hospitalized 5 times in a local hospital due to acute pancreatitis. The first episode occurred after an abdominal injury. High amylase activity was demonstrated in laboratory tests performed at that time. Abdominal ultrasound (US scan) describes heterogeneous of pancreas and enlarged of pancreatic duct. The boy had a burdened family history. His father suffered from chronic pancreatitis and his paternal grandfather had one episode of acute pancreatitis.

At the admission to the Clinic he was in a good general condition, and did not report ailments. On physical examination no abnormalities were found, laboratory tests were normal. The fat balance in the stool, C13 breath test for amylolytic function of pancreas, sweat test, determination of alpha-1 antitrypsin level were performed and all results were in normal range. US scan was similarly to previous examination. ERCP was performed. During study no pancreatic duct was contrasted, sphincterotomy was performed (fig. 1a, b). Because of family history, molecular research was performed and detected N43S mutation in *SPINK1* gene, Y318X/- in *CPA1* gene, G60G/- in *CTRC* and IVS8-5T variant in *CFTR* gene.

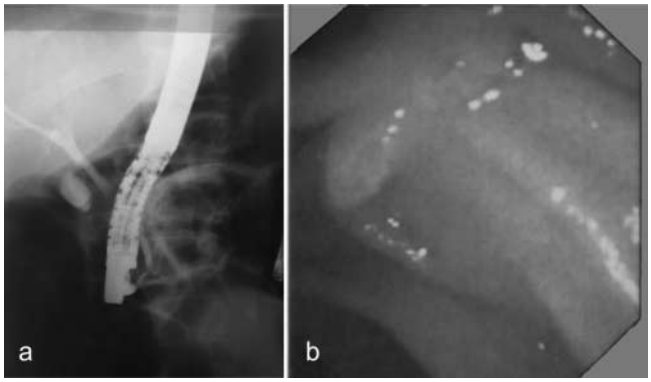

Fig. 1a, b. ERCP image. Material of the Department of Gastroenterology, Hepatology, Feeding Disorders and Pediatrics, The Children's Memorial Health Institute

After being discharged home, the boy had two episodes of acute pancreatitis. Due to the lack of improvement after standard treatment the patient was transferred back to our Clinic. Laboratory tests showed elevated inflammatory expressions with normal amylase activity. In abdominal ultrasound, heterogenous of pancreas and calcifications have been described. Diagnosis of CP was made. In order to better visualization computer tomography was performed and gallstones in the pancreatic duct were described. ERCP was used to remove the deposits. During the study, only a superficial segment of the pancreatic duct was visualized. Despite sphincterotomy, the pancreatic duct was not able to be contrasted (fig. 2a, b). To complete the diagnosis magnetic resonance cholangiopancreatography (MRCP) was performed. It describes the widening of the pancreatic duct with local narrowing and the second short pancreatic duct. On this basis the pancreas divisum was recognized. The boy had six etiological factors that could cause pancreatitis. It is difficult to decide which one was responsible for the onset of the disease.

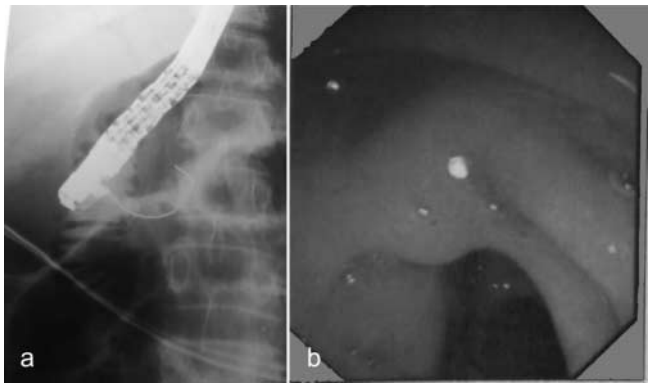

Fig. 2a, b. ERCP image. Material of the Department of Gastroenterology, Hepatology, Feeding Disorders and Pediatrics, The Children's Memorial Health Institute

DISCUSSION

Chronic pancreatitis is a multifactorial disease. There is a lot of evidence that prove the development of pancreatitis plays the role of interfering with two or

more factors, each of which can predispose to the development of the disease.

The main etiologic factors of chronic pancreatitis are gene mutations. *PRRS1* gene mutation is responsible for hereditary pancreatitis. More than 80% of patients with this mutation develop disease before the age of 20. *PRSS1* gene mutation favors early onset of exocrine and endocrine pancreatic insufficiency. The risk of developing pancreatic cancer in that group is 50-70 higher than in the general population (1). Mutation in the *PRRS1* gene is the confirmed cause of chronic pancreatitis, in contrast to other genes, which mutations only increase the risk of the disease (2). Mutations in *CPA1* gene are considered as a direct disease cause as well.

The mutations of *SPINK1* and *CTRC* genes are not a cause of pancreatitis itself, but only predisposes to the disease and requires an additional initiating factor such as trauma or infection to induce pancreatitis. It is a factor in the development of chronic pancreatitis in alcohol abusers (1).

A factor predisposing to CP development is the *CFTR* gene mutation group as well. Patients with two *CFTR* gene mutations are 40 times more likely to develop pancreatitis. In contrast, patients with *CFTR* gene mutation and *SPINK1* mutation, the risk of CP increases to 900 (3).

The second major cause that is associated with the development of chronic pancreatitis in children is an anatomical defect of the pancreatic duct. Sartiz and Meyer zum Buschenfelde describe the pancreas divisum as a direct cause of CP (4).

Another contributing factor to CP is lipid disorders, particularly familial hypertriglyceridaemia and hyperlipidemias. It has been shown that serum triglyceride levels above 500 mg/dl significantly increase the risk of pancreatitis. Probably lipid disorders do not cause CP, but only predispose to the development of this disease (5).

Another group of causes of chronic pancreatitis is biliary tract diseases. In children, the most common are: gallstones, ductal stones and primary sclerosing cholangitis. Werlin et al. described group of children with bile ducts as an important factor causing chronic pancreatitis (6). Choi et al. presented gallbladder cysts and gall bladder stones as an important cause of pancreatitis (7).

In many pediatric patients acute pancreatitis is triggered by abdominal trauma (8).

Recently there have been more and more reports about the impact of autoimmune processes on the development of pancreatitis. Naorniakowska et al. described a patient with autoimmune pancreatitis as a cause of chronic pancreatitis (9).

CONCLUSIONS

In summary, the patient we presented has more than one cause of chronic pancreatitis (abdominal trauma, gene mutations, pancreas divisum, ductal stone). It is difficult to determine which cause caused the disease to develop.

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