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Progression from acute to chronic pancreatitis associated with *CFTR* and *SPINK1* mutations

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Dear Editor

Chronic pancreatitis (CP) is commonly reported with certain genetic mutations in children [1, 2]. It is thought that acute pancreatitis (AP), acute recurrent pancreatitis (ARP) and CP are disease continuum. However, the natural history of pediatric pancreatic disease is poorly understood. We recently reported that children with ARP rapidly progress to CP and the progression is faster if they have pathogenic cationic trypsinogen (PRSS1) mutations and/or they are ≥6 years old at the first episode of AP [3]. It is not known whether other genetic mutations impact the disease progression differently.

This report is to highlight the disease progression in a child who was first diagnosed with acute pancreatitis at 10 years of age. The work-up was only positive for a heterozygous mutation in R117H and intron 8 7T and 9T poly T variants in cystic fibrosis transmembrane regulator (*CFTR*) and heterozygous N34S mutation in serine protease inhibitor Kazal type 1 (*SPINK1*). No mutation was found in *PRSS1* and chymotrypsin-C (*CTRC*) using full gene sequencing (Ambry Genetics, Aliso Viejo, CA).

During his 14-year follow-up, he had 14 documented AP episodes that required hospitalization and numerous episodes of abdominal pain that were managed at home. Only one attack was severe, requiring admission to pediatric intensive care unit. He reported abdominal pain only during AP attacks. At 23 y/o, he began experiencing frequent heartburn and indigestion. Magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) (at 17 y/o), computerized tomography (CT) scan (at 21 y/o), abdominal ultrasound (at 23 y/o) did not show changes consistent with CP.

An MRI/MRCP at 24 y/o showed irreversible changes in the pancreas consistent with CP **(**Fig. 1**).** This followed an endoscopic retrograde cholangiopancreatography (ERCP), sphincterotomy and placement of the pancreatic duct stent. After the procedure, he had significant improvement in his indigestion and overall quality of life (QOL) with increased number of pain-free days, decreased work absences due to pain, which he had not reported previously. One year after the procedure, he was admitted with another AP attack.

This case highlights the value of routine surveillance for accurate detection of CP. At the moment, the diagnosis of CP requires presence of irreversible changes in the pancreas that can only be detected by imaging studies. MRI/MRCP is an excellent modality to confirm CP [4] in children. Abdominal ultrasound provides a limited field of view [5], and may have missed CP.

The etiology of CP was most likely genetic and due to mutations in *CFTR* and *SPINK1* in this case. The role of *CFTR* and *SPINK1* mutations is well-recognized in pediatric ARP and CP [1,2,6]. If *CFTR* and *SPINK1* variants are co-inherited, earlier-onset disease, more aggressive pancreatitis and increased susceptibility to CP are expected [7]. *CFTR* 7T and 9T variants are not known to be associated with CP [8].

Endoscopic intervention provided pain relief for about a year in this patient. His response is not unusual as the endoscopic ductal decompression is known to offer short-term pain relief in CP [9]. Moreover, a recent randomized clinical study has found early

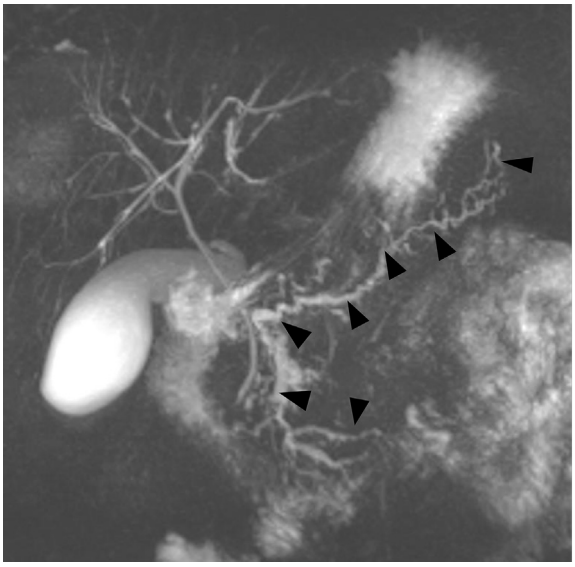

Fig. 1. Heavily T2-weighted thick-slab MRCP shows normal biliary ductal system and gallbladder. The entire pancreatic ductal system (marked by arrowheads) is beaded with segments of dilatation (main and side branches) and strictures. Together with the relatively low signal-intensity in the pancreatic parenchyma on fat-suppressed T1-weighted image (not shown), findings are consistent with chronic pancreatitis.

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surgery to be more effective in controlling pain compared to endoscopy-first approach (ESCAPE trial) [10]. Finally, this patient reported vague gastrointestinal (GI) symptoms (i.e. heartburn and indigestion), missed work days, but no obvious abdominal pain a year before the diagnosis of CP. This shows our limited understanding of pain experiences in this population and the need for uniform measurement of pain and pain-related disability.

In summary, this case highlights the importance of longitudinal follow-up in people with pancreatitis beginning in childhood, the impact of genetics in pancreatic disease progression, and the urgent need to develop assessment tools for pain, QOL, early diagnosis, and personalized therapy.

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Declaration of competing interest

Dr. Aliye Uc is a member of American Board of Pediatrics, Subboard of Pediatric Gastroenterology and Associate Editor of *Pancreatology*. Other authors have no conflicts to report.

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