Editorial Commentary

From cradle to grave: seamless management of chronic pancreatitis but consider the special requests for children

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We have read the position paper by A. Jay Freeman and the members of the Pancreas Nutrition Committee of the North American and the European Societies for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN and ESPGHAN) (1). That paper focused on chronic pancreatitis (CP) in children and endoscopic procedures about which NASPGHAN published a second position paper (2). There are clinical practice guidelines for the management of CP in adults but not for CP in children (3). Early intervention can alter the clinical course of CP in adults. Seamless management of CP in children and adults would be beneficial but we should be aware that children differ from adults, particularly in their ongoing physical and psychological growth.

CP is an irreversible advancing inflammatory and fibrotic disease with complications such as endo-/exocrine disturbance. Most adult CP cases are caused by heavy alcohol consumption, but there is a genetic component in some patients. By contrast, most children with CP have a genetic component only (4). The clinical course of hereditary CP is unclear and preventing fibrosis progression is problematic. A variety of antioxidant agents, including vitamin A, vitamin C, vitamin E, selenium, and zinc, have shown therapeutic promise for CP but have not been effective in clinical trials.

According to the mechanistic definition, fibrosis progresses because of recurrent inflammation caused by obstructive pancreatitis due to hypersecretion of pancreatic juice after a fatty meal, pancreatic ductal stricture, and pancreatic stones (5). Prevention of recurrent pancreatitis can be delaying the accumulation of fibrosis, thus improving prognosis. Early diagnosis of CP in children is necessary for improving of long-term prognosis (6). For diagnosis, we should be aware of the symptoms of early CP, acute recurrent pancreatitis, exacerbation of CP, and pancreatic pain. Diagnosis of early CP with pancreatic pain is hampered by the lack of a symptom scoring system. Actually, some cases of CP are misdiagnosed as functional dyspepsia (7). To confirm the diagnosis of CP, continuous elevation of pancreatic enzymes should be confirmed by blood testing and endoscopic ultrasound (EUS) should be performed for confirmation of fibrosis (8). However, EUS is considered as invasive procedure for children, and low-invasive examinations, such as shear-wave elastography for assessing pancreatic stiffness (9), are required for children.

Most cases of CP in children have a genetic component, but no system to examine genetic abnormalities has been established in Japan (4). A few institutions, including ours, perform genetic testing without government insurance coverage, meaning that some children with genetic-component CP are diagnosed with advanced CP. To diagnose CP in children earlier, a genetic screening

program is needed.

The management of acute pancreatitis or exacerbation of CP requires multiple ways, nutritional support, drugs, and endoscopic procedures. Dietary restriction could stunt the growth of children, necessitating a support team including a psychologist. Few drugs that prevent recurrent pancreatitis and exacerbation of CP are available. Pancreatic enzyme replacement therapy (PERT), although effective, is not a standard modality for the management of pancreatic pain. In CP cases, stricture and/or stones may cause pancreatitis or pancreatic pain by increasing the pressure in the cavity of the pancreatic duct. In such a situation, PERT is not sufficient to inhibit the secretion of cholecystokinin (CCK). However, in the experience of the first author (H Isayama), PERT is effective in patients with early CP without pancreatic ductal stricture/stones. The effect of PERT on pancreatic pain differs according to CP status/stage. In addition, PERT using a capsule that dissolves in the intestine does not inhibit the release of CCK, and nonenteric-coated formulations (i.e., powdered pancreatic enzymes) are more effective than capsule type drug for preventing pancreatitis and pain.

PERT is more important for children than for adults with CP. To promote steady growth of children, PERT enhances the absorption of nutrients and the management of pain simultaneously. To prevent/reduce recurrent pancreatitis and pancreatic pain, patients with CP tend to avoid fatty and/or large meals. Doing so does not markedly influence the health of adults but could affect the growth of children. Therefore, PERT is more important for CP in children than in adults. Typical cases of exocrine pancreatic insufficiency (EPI) showed steatorrhea or other abdominal discomfort, however, there are many mild EPI cases do not have such symptoms. The effect of PERT in mild EPI in adult is unclear but may be effective for children for growing up. PERT should be performed in children with CP and any stage of EPI.

Another promising drug for pancreatitis/pain management is camostat mesilate (8,10). In Japan, this is used to prevent pancreatitis/pain in patients with CP. Although strong evidence is lacking, this drug is prescribed regularly to adults with CP in Japan. Furthermore, gastroenterologists believe that the drug is efficacious for patients with CP complaining of pancreatic pain and recurrent pancreatitis. We typically prescribe PERT and camostat mesilate and instruct patients to increase the amount of both drugs after consuming a fatty and/or large meal or if they become aware of signs of pancreatitis occurrence. Most adult patients who do so report improvement of the frequency and severity of pancreatitis/pancreatic pain. Therefore, camostat mesilate should be evaluated for the management of pancreatic pain/pancreatitis prevention in adults and children with CP, especially early CP.

Endoscopic treatment can prevent recurrence of pancreatitis and pancreatic pain in children with CP and ductal stricture/stones, as in adults. However, endoscopic retrograde cholangiopancreatography (ERCP) procedures are more difficult in children than in adults. Adequate endoscopic treatment is required to improve the long-term prognosis (11,12) (*Figure 1*). Most endoscopists believe that endoscopic procedures in children require a specialized thin endoscope. The NASPGHN working group position paper on endoscopic procedures in children recommends that the endoscope be selected according to body weight (ERCP <10 kg, EUS <15 kg) (2). However, based on our experience, a regular endoscope can be used for infants and children (12,13). Furthermore, we perform endoscopy with pediatrician-administered sedation using a combination of ketamine, midazolam, and pentazocine without tracheal intubation by a pediatric surgeon. Easy-to-perform endoscopic procedures may improve the management and the prognosis of pancreatic inflammation and pain. If the number of pediatric endoscopists is insufficient, collaboration with adult endoscopists would improve children's quality of life (QOL) and prognosis. Accumulation of experience may reduce the hurdles to endoscopic procedures in children.

We perform EUS-guided drainage procedures for children as well. Drainage of peripancreatic fluid collection such pancreatic pseudocyst, leakage, or walled-off necrosis after severe pancreatitis was formerly performed (13). However, some cases require EUS-guided pancreatic ductal drainage (EUS-PDD); these include difficult transpapillary endoscopic intervention, cannulation failure, failed passage of the pancreatic ductal stricture to the papilla due to duodenal stricture, and surgically altered anatomy. EUS-PDD can be performed in children with a dilated pancreatic duct (14). *Figure 2* shows the treatment of traumatic pancreatic ductal disruption with pancreatic leakage by EUS-guided cyst and pancreatic duct drainage (same case as reference 14 but showed different images). We also have published a case report of treatment of recurrent cholangitis caused by a stricture at the site of choledochojejunostomy by EUS-guided hepaticogastrostomy in a 7-year-old girl (15). EUS-guided-celiac plexus/ganglion neurolysis can also

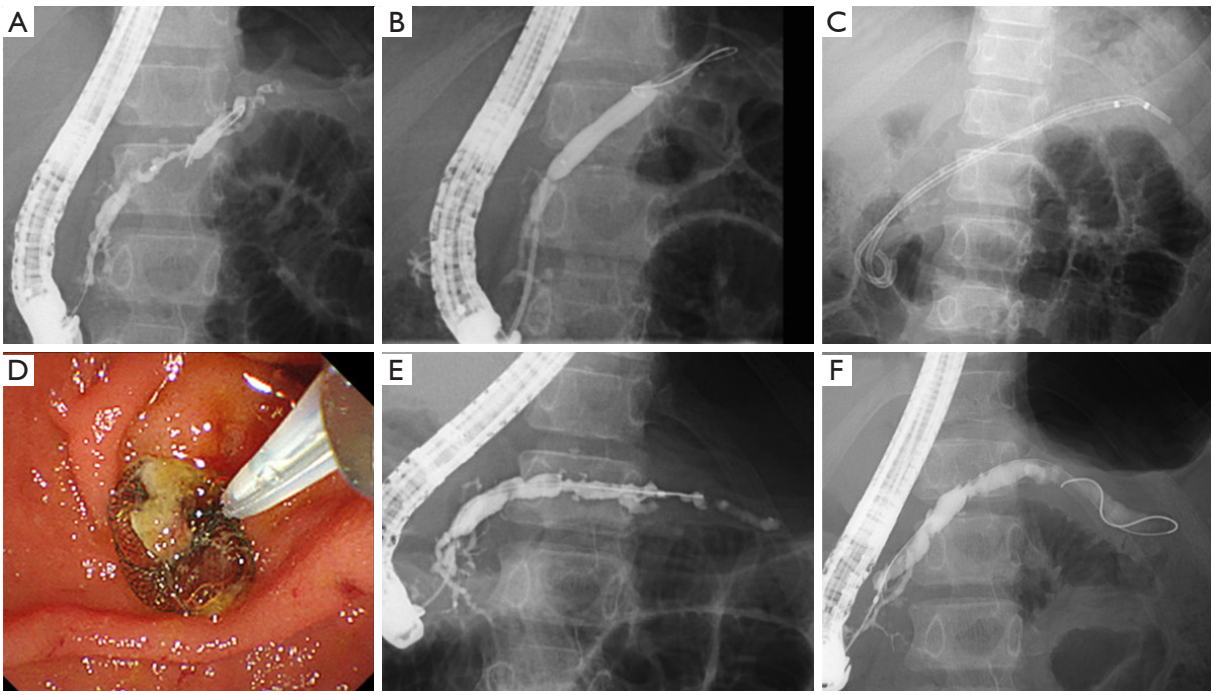

Figure 1 Endoscopic treatment for idiopathic chronic pancreatitis in a 10-year-old boy. (A) ERCP revealed diffuse pancreatic duct stricture. (B) Dilation of the stricture using a 6-mm balloon. (C) Placement of two 7-Fr single-pigtail stents to dilate the stricture. (D) Removal of pancreatic stones using a basket catheter. (E,F) Pancreatic duct stricture was gradually improved by repeated balloon dilation and insertion of multiple stents. ERCP, endoscopic retrograde cholangiopancreatography.

be performed and is less invasive than percutaneous interventions.

Many of the specialists, drugs, procedures, and devices used to manage CP in adults can be applied to children. Seamless management from children to adults can be realized by collaboration among pediatricians, gastroenterologists, and endoscopists, with support from nutritionists, psychologists, and pain clinicians. The most important issue is the establishment of a diagnostic strategy for early CP. Discussions among pediatricians, gastroenterologists, endoscopists, radiologists, and genetic specialists will facilitate the formulation of diagnostic criteria for early CP, which would improve the prognosis of CP in children.

In conclusion, seamless management of CP in children and adults would be beneficial. Many examinations/treatments for adults can also be used for children. However, it is important to be aware that children differ from adults, particularly in their ongoing physical and psychological growth.

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Footnote

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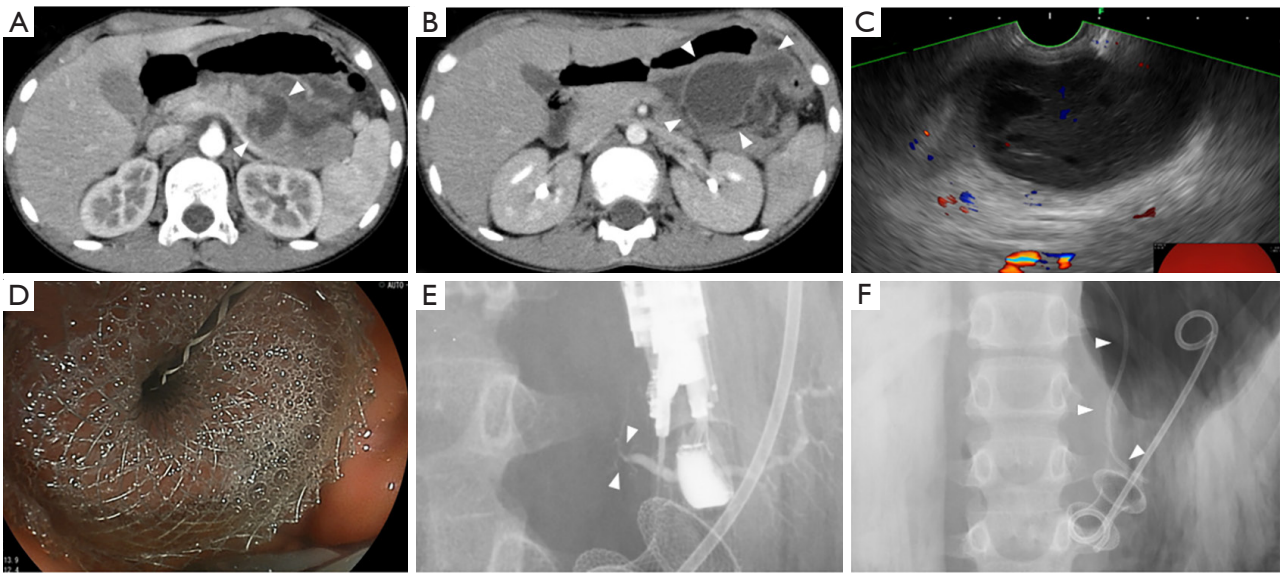

Figure 2 EUS-guided procedures for a 10-year-old boy with a traumatic main pancreatic duct injury [same case as reference (14) but showed different images]. (A) Enhanced CT image of pancreatic transection (arrowheads) due to traumatic main pancreatic duct injury. (B) Enhanced CT showing fluid collection around the pancreatic transection 3 weeks after the injury (arrowheads). (C) Endosonographic image of fluid collection. (D) Endoscopic image: a LAMS was deployed into the fluid. (E) Fluoroscopic image: The main pancreatic duct was disconnected as a result of the injury (arrowheads). The slightly dilated distal main pancreatic duct was punctured using a 19-G needle. (F) Fluoroscopic image: EUS-guided Pancreatogastrostomy with a 5-Fr plastic stent (arrowheads). EUS, endoscopic ultrasound; CT, computed tomography; LAMS, lumen-apposing metal stent.

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