OPEN

CFTR p.F508del Mutation Carrier Status Is Not Associated With Biliary Acute Pancreatitis

To the Editor:

The cystic fibrosis transmembrane conductance regulator (CFTR) channel is highly expressed in the biliary tree and the gall bladder, and maintains biliary health through a protective "bicarbonate umbrella."[1] Cystic fibrosis (CF) disease caused by homozygous loss-of-function mutations in *CFTR* is associated with biliary disorders in a subset of patients.[1,2] Therefore, we hypothesized that carrier status for a severe CF-causing *CFTR* mutation might increase risk for biliary acute pancreatitis. A Polish study found no association between the p.F508del *CFTR* variant and biliary acute pancreatitis; however, the investigated cohort was small.[3] Here, we genotyped Hungarian patients with biliary acute pancreatitis, nonbiliary acute pancreatitis, and healthy controls for the c.1521_1523delCTT (p.F508del) mutation by direct Sanger sequencing of exon 11 in *CFTR*. Patients with chronic pancreatitis, those with recurrent acute pancreatitis with more than 2 attacks, and subjects older than 60 were excluded. The biliary pancreatitis cohort included 190 subjects (117 women); the mean age at time of admission was 43.8 years (standard deviation, 11.5 years; range, 18–60 years), the disease severity was mild in 151 cases (98 women), moderate in 34 cases (17 women), and severe in 5 cases (2 women). The nonbiliary pancreatitis cohort consisted of 178 patients (51 women); the mean age at time of admission was 44.3 years (standard deviation, 9.9 years; range, 18–60 years); and disease severity was mild in 105 cases, moderate in 62 cases, and severe in 11 cases. The etiology in this cohort was alcoholic in 81 subjects (6 women), idiopathic in 60 subjects (38 women), hypertriglyceridemia associated in 26 subjects (6 women), and post-endoscopic retrograde cholangiopancreatography complication in 11 subjects (1 woman). The control group included 197 subjects (74 women), and the mean age at the time of blood collection was 37 years (standard deviation, 8.5 years; range, 24–59 years).

We found the heterozygous p.F508del variant in 6 of 190 patients (3 women) with biliary acute pancreatitis (3.2%), in 4 of 178 patients (all men) with nonbiliary acute pancreatitis (2.2%), and in 5 of 197 controls (2.5%, 1 woman). As expected, no homozygous p.F508del carriers were detected. All patients with p.F508del in the biliary group had mild disease, whereas in the nonbiliary group, 3 had mild disease (2 alcoholic, 1 idiopathic) and 1 had severe disease of alcoholic etiology. Comparison of carrier frequencies revealed no significant association of the p.F508del variant with acute pancreatitis. The calculated odds ratios (OR) with 95% confidence intervals (CI), and *P* values were as follows—biliary acute pancreatitis versus controls: OR, 1.25; 95% CI, 0.38–4.17, $P = 0.71$; nonbiliary acute pancreatitis versus controls: OR, 0.88; 95% CI, 0.23–3.34, $P = 0.85$; combined acute pancreatitis cohort versus controls: OR, 1.07; 95% CI, 0.36–3.18, $P = 0.9$.

We conclude that heterozygous CF-causing *CFTR* mutations do not modify susceptibility for biliary acute pancreatitis.

The authors declare no conflict of interest. This work was supported by the Eötvös Loránd Research Network award 460051 and a grant from the Research Fund of the University of Pécs to E.H.; the National Institutes of Health (NIH) grant R01 DK082412 to M.S.T.; the János Bolyai Research Grant (BO/00648/21/5), the EU's Horizon 2020 research and innovation grant 739593, and the New National Excellence Program (UNKP-21-5-SZTE-551) to B.C.N.; the National Research Development and Innovation Office grant K131996, the Economic Development and Innovation Operative Programme Grant GINOP 2.3.2-15-2016-00048, the Human Resources Development Operational Programme Grant EFOP-3.6.2-16-2017-00006, and an ITM-NRDIF grant (TKP2021-EGA-23) to P.H; the National Research, Development and Innovation Office Grant FK138929 and the Cystic Fibrosis Trust Strategic Research Center Grant NU000600 to AP.

Ágnes Rita Martonosi, MD
Heim Pál National Pediatric Institute
Budapest, Hungary
Doctoral School of Clinical Medicine
University of Szeged
Szeged, Hungary
Institute for Translational Medicine
University of Pécs Medical School
Pécs, Hungary

Balázs Csaba Németh, MD, PhD
Hungarian Centre of Excellence for Molecular Medicine University of Szeged
Translational Pancreatology Research Group
Szeged, Hungary
Department of Medicine
Albert Szent-Györgyi Medical School
University of Szeged
Szeged, Hungary

Andrea Párniczky, MD, PhD
Heim Pál National Pediatric Institute
Budapest, Hungary
Institute for Translational Medicine
University of Pécs Medical School
Pécs, Hungary
Centre for Translational Medicine
Semmelweis University
Budapest, Hungary

Áron Vincze, MD, PhD
Division of Gastroenterology
First Department of Medicine
University of Pécs Medical School
Pécs, Hungary

Andrea Szentesi, PhD
Institute for Translational Medicine
University of Pécs Medical School
Pécs, Hungary

Bálint Erőss, MD, PhD
Institute for Translational Medicine
University of Pécs Medical School
Pécs, Hungary
Centre for Translational Medicine
Semmelweis University
Budapest, Hungary
Institute of Pancreatic Diseases
Semmelweis University
Budapest, Hungary

Miklós Sahin-Tóth, MD, PhD
Department of Surgery
University of California, Los Angeles
Los Angeles, CA

Péter Hegyi, MD, PhD, DSc, MAE
Institute for Translational Medicine
University of Pécs Medical School
Pécs, Hungary
Centre for Translational Medicine
Semmelweis University
Budapest, Hungary
Institute of Pancreatic Diseases
Semmelweis University
Budapest, Hungary
Translational Pancreatology Research Group
Interdisciplinary Centre of Excellence for Research Development and Innovation

University of Szeged
Szeged, Hungary

Eszter Hegyi, MD, PhD
Doctoral School of Clinical Medicine
University of Szeged
Szeged, Hungary
Institute for Translational Medicine
University of Pécs Medical School
Pécs, Hungary
eszter.hegyi@aok

REFERENCES

1. Assis DN, Debray D. Gallbladder and bile duct disease in cystic fibrosis. *J Cyst Fibros*. 2017; 16(suppl 2):S62–S69.
2. Curry MP, Hegarty JE. The gallbladder and biliary tract in cystic fibrosis. *Curr Gastroenterol Rep*. 2005;7: 147–153.
3. Koziel D, Gluszek S, Kowalik A, et al. Genetic mutations in *SPINK1*, *CFTR*, CTRC genes in acute pancreatitis. *BMC Gastroenterol*. 2015; 15:70.

Widespread Hyperalgesia by Pancreatic Quantitative Sensory Testing Is Associated With Reduced Pain Response in Chronic Pancreatitis

To the Editor:

Chronic pancreatitis (CP) is a debilitating fibroinflammatory disease in which abdominal pain is reported by up to 80% of patients during their disease course and treatment options are limited to symptom control.[1] Patients with evidence of pancreatic duct obstruction may be offered invasive treatments to relieve pain suspected to be due to intraductal hypertension.[1] However, satisfactory pain relief after invasive treatments is unpredictable[1] and achieved in only a subset of patients. This is probably explained by other pain mechanisms being operative in these cases including sensitization of central pain pathways.[2]

Pancreatic quantitative sensory testing (P-QST), a novel application of nociceptive testing, can stratify patients with CP into distinct phenotypes.[3,4] These phenotypes include patients with increased pain sensitivity to experimental pain stimuli applied in the upper abdominal area sharing spinal segmental innervation with the pancreas (segmental hyperalgesia) and patients with evidence of generalized hyperalgesia to experimental pain stimuli applied at body segments remote to the pancreas (widespread hyperalgesia). Segmental or widespread hyperalgesia can be used as a biomarker of sensitization of central pain pathways.[4] Widespread hyperalgesia probably reflects a more chronic state of central sensitization considered less responsive to treatment.

In this pilot study of 48 patients with painful CP scheduled for pancreas directed invasive treatments, we hypothesize that evidence of widespread hyperalgesia by P-QST (suggestive of widespread central sensitization) will be associated with lower likelihood to achieve adequate pain relief.

Eligible patients 18 years or older, with abdominal pain of intensity ≥3 (numeric rating scale, 0–10) because of definite CP (Cambridge III or IV), were prospectively enrolled between October 2017 and June 2021 in this multicenter pilot study from the University of Pittsburgh Medical Center (IRB STUDY20050053), Johns Hopkins Medical Institutions (IRB 00143375), and Indiana University Medical Center (IRB 1909843967) (registered with Clinicaltrials.govNCT03434392).

Assessment of P-QST was performed before planned invasive treatment using our previously published P-QST protocol.[3,5] Patients were categorized into 1 of 3 subgroups: no hyperalgesia, segmental hyperalgesia, or widespread hyperalgesia.[4] All patients underwent invasive treatment for painful CP, including endoscopic retrograde cholangiopancreatography with or without extracorporeal shock-wave lithotripsy and/or pancreatic duct stent placement, or surgical treatment (pancreaticoduodenectomy or total pancreatectomy with islet cell autotransplantation). Clinical pain scores (10-point numeric rating scale) was obtained at baseline and follow-up 6 months after the invasive procedure. Pain response was defined as the relative change in pain scores comparing postprocedural versus baseline pain scores. Distributions of pain response and P-QST phenotypes were explored in a graphical analysis using a frequency plot.

A total of 48 patients (22 male; median age, 47 years [range, 18–73 years]) were recruited. Alcohol etiology of CP was present in 26 patients (54%). Distribution of P-QST phenotypes at baseline included the following: 23 (48%), no hyperalgesia; 18 (38%), segmental hyperalgesia; and 7 (15%), widespread hyperalgesia. Endoscopic treatment (endoscopic retrograde cholangiopancreatography±extracorporeal-shock-wave lithotripsy) was performed in 33 patients, and 15 underwent pancreatic surgery (total pancreatectomy with islet cell autotransplantation, n = 14; Whipple, n = 1). An increased density of patients with widespread hyperalgesia was observed among patients with limited pain response or worsening of pain after 6 months (Fig. 1). A total of 3 of 28 patients (10.7%) in the group with favorable pain response had widespread hyperalgesia. In the group of patients with nonfavorable pain response (nonresponse or worsening of pain), the proportion of patients with widespread hyperalgesia was 4 of 20 patients (20.0%).

Pain phenotyping tools to appropriately select CP patients for targeted therapy have been underdeveloped. Treatment decisions often depend on the appearance of the pancreas on cross-sectional imaging despite the fact that imaging findings do not correlate with pain experience in CP or predict response after invasive treatment.[6] Over half of patients sent for directed therapy via invasive treatment for painful CP, regardless of endoscopic or surgical nature of treatment, may not benefit.[7] Surgical treatments for CP in particular are associated with high risk of morbidity and, in some patients, may result in additional postoperative pain.[1,8] Because of significant risks, invasive treatment should be carefully considered in each patient before it is undertaken.

The role of widespread hyperalgesia in painful CP has not yet been fully harnessed for its ability to differentiate patients whose pain may respond to invasive treatment from those whose pain is likely to continue independent of technical successful invasive therapy.[1] Although the results in the present study were not subjected to formal statistical analysis because of the limited number of patients with widespread hyperalgesia (n = 7), we envision the presence of widespread hyperalgesia as a potential clinical useful predictor of response to invasive treatment pending further evaluation in prospective clinical studies.[1,9] However, additional factors including demographics, clinical characteristics, and psychosocial factors are also likely also to influence response to treatment.[10] Likewise, type of invasive therapy may also affect response to treatment. Analgesic agents have the potential to impact the pain experience including P-QST phenotype; however, analgesic influence on the current pain state must be taken into account, and therefore, patients should still be using their clinically indicated medications when undergoing P-QST testing for its use in predicting outcome to invasive therapy. Multivariable prediction models including P-QST and other parameters are currently being evaluated within the Pancreatic Pain Consortium.

By identifying patients who are less likely to respond to invasive treatment, patient selection for available treatments can be optimized, and alternative lower-risk treatments can be pursued. This development has the potential to effectively target therapy, thereby reducing the overall morbidity of treatment for this challenging patient population.