Digestive and Liver Disease 53 (2021) 1294–1300

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Comparison of idiopathic recurrent acute pancreatitis [IRAP] and recurrent acute pancreatitis with genetic mutations ☆,☆☆,★

Luisa M. Cruz [a], Joshua Y. Kwon [b], Sven P. Oman [b], Himesh Zaver [b], Gabriel A. Bolaños [c], Paul T. Kröner [d], Massimo Raimondo [d], Yan Bi [d], Frank J. Lukens [d], Juan E. Corral [e,*]

[a] Universidad Francisco Marroquin - School of Medicine, Guatemala City, Guatemala
[b] Department of Internal Medicine, Mayo Clinic, Jacksonville, Florida, USA
[c] Department of Internal Medicine, University of South Alabama, Mobile, Alabama, USA
[d] Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, Florida, USA
[e] Division of Gastroenterology and Hepatology, Presbyterian Healthcare Services, Albuquerque, New Mexico, USA

ARTICLE INFO

Article history:
Received 30 December 2020
Revised 13 April 2021
Accepted 14 April 2021
Available online 7 May 2021

Keywords:
Acute pancreatitis
Chronic pancreatitis
ERCP
Opioids
Gene mutations

ABSTRACT

Background: Idiopathic recurrent acute pancreatitis (IRAP) describes frequent episodes of pancreatitis without an etiology found using current testing. We compared the natural history of IRAP with recurrent acute pancreatitis with genetic mutations.
Methods: Retrospective cohort of patients with recurrent acute pancreatitis (≥2 episodes) and negative conventional testing. All patients had ≥1 episode after cholecystectomy and completed genetic testing. Primary outcomes were chronic pancreatitis incidence, pancreatic cancer, and mortality. Secondary outcomes included opioid and ERCP utilization.
Results: 128 patients met criteria for presumed IRAP. 35 patients met criteria for true IRAP. 12 patients had recurrent acute pancreatitis with gene mutations. Chronic pancreatitis developed in 27 (77.1%) IRAP patients over a median of 6 years. Chronic pancreatitis incidence was similar in IRAP and CFTR mutation carriers; but developed later in SPINK1 carriers. No patients developed pancreatic cancer or died from pancreatic-related causes. Patients were frequently treated with oral opioids and ERCP, without significant differences within or between groups.
Conclusion: IRAP and pancreatitis in mutation carriers is associated with chronic pancreatitis. Important differences in natural history were observed, but no association was found with cancer or pancreas-related mortality. Efforts to understand the genetic contributions to IRAP, minimize opioids and unnecessary ERCPs are encouraged.

1. Introduction

Idiopathic recurrent acute pancreatitis (IRAP) is an evolving term that describes recurrent episodes of acute pancreatitis without a clear etiological factor identified. Definitions have varied across time and are inherently limited to our understanding of the pathophysiologic mechanisms why patients develop acute pancreatitis. [1,2] Recurrent acute pancreatitis (or relapsing acute pancreatitis) is defined as two or more episodes of acute pancreatitis and is relatively common with an incidence of 8–10 cases per 100,000. [3] Routine imaging and laboratory testing can identify a cause in 70–90% of cases. Most cases being secondary to gallstone disease and alcohol. [4–6] If no cause is identified, research shows that these patients are more likely to have three or more recurrent episodes. [7,8] The appropriate diagnostic testing for recurrent pancreatitis has been described in different guidelines yet the optimal sequence to use available testing, and the treatment interventions for some etiologies remains an area of debate. [9]

After only one episode of acute pancreatitis, some patients develop permanent changes in the pancreatic ducts (without acinar changes) and other patients experience a prolonged course of interstitial pancreatitis (smouldering pancreatitis). [1] Similarly, the first episode of acute pancreatitis may trigger a necrosis-fibrosis sequence with dysfunctional repair mechanisms leading to chronic

Abbreviations: BMI, Body mass index; EMR, Electronic medical record; ERCP, Endoscopic Retrograde Cholangiopancreatography; EUS, Endoscopic ultrasound; IPMN, Intraductal papillary mucinous neoplasm; IQR, Interquartile range; IRAP, Idiopathic recurrent acute pancreatitis; MRI, Magnetic resonance imaging; US, Ultrasound.

☆ Grant support: None.
☆☆ Transcript profiling: None.
★ Writing assistance: None.
* Corresponding author.
E-mail address: jcorralhu@phs.org (J.E. Corral).

https://doi.org/10.1016/j.dld.2021.04.013
1590-8658/

pancreatitis. [7] The overlap of different healing processes challenge the distinction of smouldering pancreatitis, early chronic pancreatitis and IRAP; and support the idea that pancreatitis represents a disease spectrum (known as the "sentinel acute pancreatitis event" or SAPE hypothesis). [1,10]

Over the last 30 years new mechanisms of pancreatitis have been identified including medications toxicity, gene mutations and viral infections. [6] In addition, the contribution of undiagnosed gallstone disease or microlithiasis has been stressed by the reduced rates of idiopathic acute pancreatitis seen after cholecystectomy. [11] We aim to describe the natural course of IRAP, using individual-level data and most recent definitions, and compare long term outcomes including chronic pancreatitis, pancreatic cancer and death from pancreas-related complications. Our secondary objective is to compare IRAP with those patients with recurrent pancreatitis and relevant genetic mutations.

2. Materials and methods

We evaluated a retrospective cohort of patients with recurrent episodes of acute pancreatitis and complete genetic testing in any of the three Mayo Clinic Hospitals (Arizona, Florida and Minnesota). A search was conducted using an electronic cohort generator looking for all patients who had two or more episodes of acute pancreatitis and underwent genetic testing from January 1st 1999 to December 31st 2019. Study design and reporting adhered to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations (Appendix A). [12]

Acute pancreatitis was defined using the revised Atlanta diagnostic criteria. [4] IRAP was defined following the IAP/APA guidelines [9] and the proposed algorithm from the Dutch Pancreatitis Study Group with a few modifications. [11] Patients must have two or more episodes of acute pancreatitis not related to endoscopic retrograde cholangiopancreatography (ERCP). Presumed IRAP was defined by diagnosing idiopathic acute pancreatitis after the standard evaluation (family history, laboratory tests and abdominal ultrasound). Patients with any history of alcohol use (based on chart review) were excluded regardless of use duration, or amount (i.e. excluding patients with alcohol use described as "remote", "minimal" and "social"). Hypertriglyceridemia, autoimmune pancreatitis, drug induced pancreatitis, trauma and other etiologies were excluded based on chart review. True IRAP was defined by adding negative additional imaging and genetic testing. We required for one episode of acute pancreatitis to develop after having a cholecystectomy. Presence of biliary sludge or stones was documented based on imaging including endoscopic ultrasound (EUS), ERCP, magnetic resonance imaging (MRI), or surgical reports. Gene mutation carriers with a clear insult causing pancreatitis were classified by the presumed insult (e.g. alcohol use) and excluded from analysis. We excluded all patients with concerns of chronic pancreatitis during the index episode, but recorded the first time any provider added chronic pancreatitis to the diagnoses in our electronic medical records (EMR).

Four investigators (SPO, HZ, JK and LMC) individually reviewed the medical records to confirm an accurate diagnosis of IRAP. Data collected included demographics, first pancreatitis episode, date of cholecystectomy, date of first ERCP, date of oral opioid prescription, relevant test results (i.e. genetic mutations, A1C, triglyceride, calcium, and tissue transglutaminase levels), relevant imaging, pancreatic cancer diagnosis, cancer family history, clinical suspicion of chronic pancreatitis, and survival. If an exact date was unavailable, it was rounded to the middle day of the month and the middle month of the year.

The primary outcomes were chronic pancreatitis incidence (as recorded by the treating physician or radiology reports), pancreatic cancer incidence and mortality (i.e. pancreatitis-related mortality and all-cause mortality). Secondary outcomes were oral opioid utilization, ERCP completion, and ERCP related pancreatitis.

Cohort period time started the day of the first episode of acute pancreatitis. Oral opioid use was counted from the first day oral opioids were prescribed. There was no verification of opioid use or compliance. Inpatient doses of intravenous opioids were not recorded. Genetic testing was completed using a hereditary pancreatitis panel that tests for four gene mutations (i.e. PRSS1, SPINK1, CFTR and CTRC genes). This commercial panel uses custom sequence capture and targeted next-generation sequencing followed by polymerase chain reaction, and Sanger sequencing and gene dosage analysis.

Traditional nomenclature uses "hereditary pancreatitis" to describe all patients with family history of pancreatitis following an autosomal inheritance pattern (e.g. seen in PRSS1 gain-of-function mutations), and "familial pancreatitis" for those patients with recessive patterns, non-mendelian or complex inheritance patterns. Considering that few patients had complete familial history we opted to use the term "recurrent acute pancreatitis with a genetic mutation" and avoided using these other two terms.

2.1. Statistical analysis

Descriptive statistics are presented for patients with IRAP and patients with recurrent pancreatitis and a known genetic mutation. Categorical data was compared with Pearson's chi-squared test and continuous data with standard t-test.

Incidence rates are reported as unadjusted rates per patient-years. Incidence rates among the two groups were compared using Kaplan-Meier curves and log-rank tests. Small sample size precluded multivariate analysis to evaluate the effects of patient characteristics on developing chronic pancreatitis, cancer, or survival. For the analysis evaluating the incidence of chronic pancreatitis, follow-up cohort duration was right censored to 25 years to minimize the effects of loss to follow-up.

Data were analyzed using Stata 14.0 MP (Stata-Corp, College Station, TX, USA). All tests for significance were two sided and p values less than 0.05 were considered significant. The research protocol approved by the Mayo Clinic Institutional Review Board (No. 19-011337). No patients were contacted during this study.

3. Results

Initial review identified 21,325 patients treated for acute pancreatitis in the three hospitals between 1999-2019. We recorded 128 patients meeting our criteria for presumed IRAP who underwent genetic testing. After detailed chart review 35 patients met criteria for true IRAP. Twelve more patients had recurrent acute pancreatitis attributed to genetic mutations (eight CFTR, two SPINK1, one PRSS1 and one with combined CFTR and SPINK1 mutations). Patient inclusion flow is summarized in Fig. 1. Patients were followed for a median follow-up time of 6 years (interquartile range [IQR] 4–12 years).

Patient demographics and presentation are summarized in Table 1. IRAP patients had a median of 4 pancreatitis episodes (IQR 2-5) during the cohort. Two patients with IRAP had 11 documented episodes each. Patients in the second group (recurrent acute pancreatitis and a genetic mutation) had a median of 4 pancreatitis episodes (IQR 2-6.5). One patient had a total of 9 documented episodes in this second group. Patients with a genetic mutation on genes PRSS1 or SPINK1 developed their first episode of acute pancreatitis at a younger age compared to their peers with IRAP (log-rank test $p < 0.001$). There was no difference in age of presentation (first pancreatitis episode) between patients with CFTR mutation and IRAP. (Fig. 2)

Table 1
Characteristics of patients with IRAP and recurrent acute pancreatitis with a known genetic mutation. $N = 47$.

	IRAP N=35	PRSS1 N=1	SPINK1[a] N=3	CFTR N=8
Gender, male (%)	12 (33.3)	0 (0.0)	2 (66.7)	2 (25.0)
BMI, median (IQR)	27 (22-33)	17	21 (21-23)	25 (22-27)
Previous tobacco use, n(%)	9 Smoking (25.0) 2 Chewing (5.6)	1 Smoking (100.0)	0 (0.0)	2 Smoking (25.0)
Marijuana use, n(%)	3 (8.3)	0 (0.0)	0 (0.0)	1 (12.5)
Oral opioid use, n(%)[b]	25 (71.4)	1 (100.0)	1 (33.3)	6 (75.0)
Laboratories				
Triglyceride level, median mg/dL (IQR)[b]	122 (87-161)	58	72.50	130.5 (113-175.5)
IgG4 level, median mg/dL (IQR)[b]	7.5 (0.0-31.0)	20.3	105.0	15.2 (8.9-22.5)
Tissue transglutaminase, normal (%)[b]	18 (94.7)	1 (100.0)	1 (100.0)	4 (100.0)
A1C, median (IQR)	5.5 (4.9-6.3)	5.8	5.4	5.4 (5.0-5.5)
Imaging				
Pancreas divisum, n(%)	9 (25.0)	0 (0.0)	1 (33.3)	1 (12.5)
IPMN, n(%)	5 side branch cysts (13.9)	0 (0.0)	0 (0.0)	2 side branch cysts (25.0)
Biliary sludge and stones				
Ruled out with abdominal US, n(%)	2 (5.7)	0 (0.0)	0 (0.0)	2 (25.0)
Ruled out with EUS/ERCP, n(%)	15 (42.9)	1 (100.0)	0 (0.0)	2 (25.0)
Ruled out with MRI/MRCP, n(%)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)
Ruled out with imaging but found during cholecystectomy, n(%)	3 (8.6)	0 (0.0)	0 (0.0)	3 (37.5)
Not data available, n(%)	14 (40.0)	0 (0.0)	3 (100.0)	1 (12.5)
Acute pancreatitis				
Age first episode, median (IQR)	30 (19–43)	4	14 (12–25)	35 (17–47.5)
Number of episodes, median (IQR)	4 (2–5)	4	2 (2–8)	4.5 (3–6.5)
Follow-up time, median years (IQR)	5 (3–11)	26	22 (14–35)	6 (4–11)

Abbreviations: BMI: Body mass index, ERCP: Endoscopic retrograde cholangiography, EUS: Endoscopic ultrasound, IPMN: Intraductal papillary mucinous neoplasm, IQR: Interquartile range, IRAP: Idiopathic recurrent acute pancreatitis, MRI: Magnetic resonance imaging, US: Ultrasound.
[a] One patient with both SPINK-1 and CFTR mutations is included in the SPINK group here. No patients had CTRC mutation.
[b] Calculated based on patients with available information (e.g. patients receiving the test).

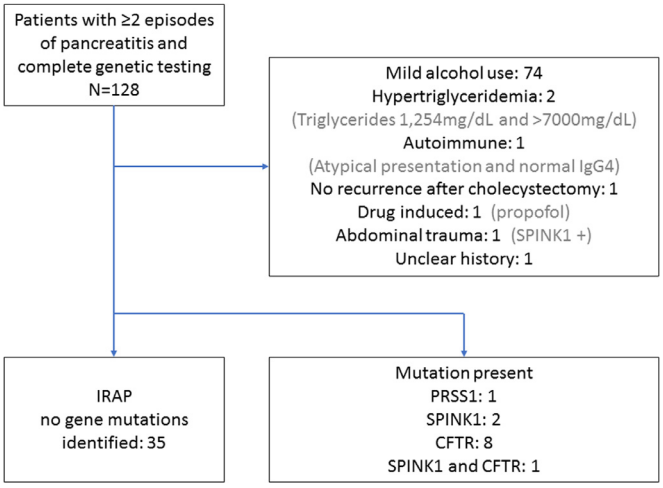

Fig. 1. Patient inclusion flowchart.

Details of the genetic mutations identified are provided in Supplement Table. CFTR gene testing showed variability in intron 8 (27 patients had poly T alleles: 7T/7T, 9 patients had poly T alleles: 5T/7T, and 8 patients had poly T alleles: 7T/9T) and intron 9 (6 had poly T alleles: 7T/7T, and 1 had poly T alleles: 5T/9T).

3.1. Primary outcomes

Chronic pancreatitis developed in 36 (76.6%) patients over a median of 4 (IQR 1-8) years after the first episode of acute pancreatitis. There was no significant difference in chronic pancreatitis incidence between patients with IRAP and recurrent acute pancreatitis with a known genetic mutation (10.6% per year and 5.3% per year respectively, log-rank test $p = 0.15$). Chronic pancreatitis developed similarly among patients with IRAP and patients with a CFTR mutation, however, chronic pancreatitis developed significantly later in patients with SPINK1 mutation (log-rank test $p = 0.04$) (Table 2, Fig. 2).

No patients developed pancreatic cancer or died from pancreatitis-related complications during our study period. One

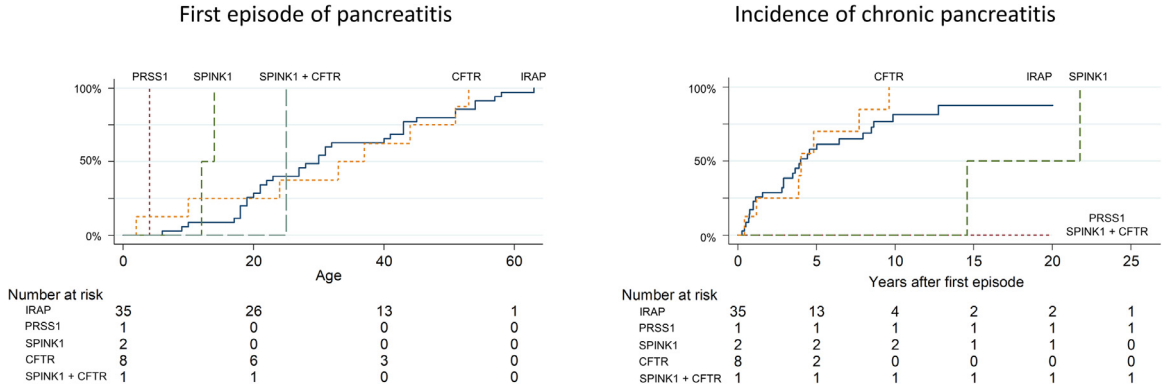

Fig. 2. First episode of acute pancreatitis and incidence of chronic pancreatitis among patients with IRAP and recognized genetic mutations.
Footnote: IRAP: Idiopathic recurrent acute pancreatitis.

Table 2
Clinical outcomes among cohort patients. *N*=47

	IRAP *N*=35	Recurrent acute pancreatitis with mutations *N*=12	p
Chronic pancreatitis			
Cases (%)	27 (77.1)	9 (75.0)	0.9[b]
Cumulative follow-up[a]	254 years	169 years	
Crude incidence	10.6% per year	5.3% per year	0.15[c]
Fecal elastase	2 tested and normal	1 tested with moderate exocrine insufficiency	
Pancreatic cancer			
Cases (%)	0 (0.0)	0 (0.0)	NA
Crude incidence	0 per year	0 per year	
Family history of pancreatic cancer (%)	7 (20.0)	5 (41.7)	
Mortality			
Pancreatitis-related deaths	0 (0.0)	0 (0.0)	NA
All-cause deaths	1 (2.9)	0 (0.0)	
Crude mortality	0.4% per year	NA	

Abbreviations: IRAP: Idiopathic recurrent acute pancreatitis NA: Not available.
[a] Adding all years of all members in the cohort
[b] Pearson's Chi square test
[c] Log rank test

Table 3
Healthcare utilization among cohort patients. *N*=47.

	IRAP *N*=35	Recurrent acute pancreatitis with mutations *N*=12	p
Oral opioid use			
Ever user (%)	25 (71.4)	8 (66.7)	0.7
Duration, median months (IQR)[a]	30 (15-64)	97 (51-256)	0.007
ERCP			
Performed (%)	26 (74.3)	8 (66.7)	0.6
Interval first episode-to-ERCP, median months (IQR)[b]	24 (8-57)	45 (12-228)	0.2
ERCP-related pancreatitis, n(%)[c]	13 (41.9)	6 (66.7)	0.2
Cholecystectomy			
Performed (%)	35 (100.0)	12 (100.0)	NA
Surgery prior to index pancreatitis, median months (IQR)[d]	9 patients: 64 (24-94)	1 patient: 24	
Surgery posterior to index pancreatitis, median months (IQR)	26 patients: 4 (1-64)	11 patients: 6 (2days-178)	

Abbreviations: ERCP: Endoscopic retrograde cholagiopancreatography, IQR: Interquartile range, IRAP: Idiopathic recurrent acute pancreatitis.
[a] Two patients were taking oral opioids prior to index acute pancreatitis (over 6 months and 103 months).
[b] One patient had an ERCP performed prior to index acute pancreatitis (2 months). Three patients had their first ERCP to treat index acute pancreatitis (<1 month of first episode).
[c] Calculated on those who underwent an ERCP
[d] Eight patients had their cholecystectomy during their first acute pancreatitis episode (all <28 days of index acute pancreatitis diagnosis).

male patient with microcephaly, cerebral palsy, and epilepsy died at age 19 from non-pancreatic causes. Death was attributed to *Clostridioides* colitis, sepsis and thrombocytopenia-associated multiple-organ failure.

3.2. Opioid use and endoscopic retrograde pancreatography (ERCP)

Details on medications and analgesics were available for 30 IRAP patients (date of first prescription could not be clearly established in 5 patients). Two patients were taking oral opioids prior to index acute pancreatitis episode (6 months and 103 months prior). Duration of oral opioid medications and ERCP completion are illustrated in Table 3 and Fig. 3. Besides shorter use of oral opioids in patients with IRAP compared to those with an identified genetic mutation, no other significant differences were noted within both groups.

Three quarters of patients underwent an ERCP for different reasons. One patient had an ERCP performed two months prior to index acute pancreatitis (performed for abdominal pain, acholic stools, and elevated liver enzymes). Three patients had their first ERCP as part of the treatment for the index acute pancreatitis (<1 month of first episode). Approximately half of the patients in both groups experienced at least one hospitalization for ERCP-related pancreatitis. ERCP-related pancreatitis was more frequent in patients with a genetic mutation (6 [66.7%]) than in patients with IRAP (13 [41.9%]) without reaching statistical significance ($p = 0.2$).

3.3. Additional findings

On our initial review three patients with SPINK1 mutations had additional insults that potentially triggered the first episode of acute pancreatitis: one had hypertriglyceridemia (highest triglyceride level was 1,254 mg/dL), one had trauma leading to recurrent pancreatitis and one more had a second mutation in the CFTR gene.

Three patients with a gene mutation (One SPINK1, one CFTR +, and one with combined SPINK1 and CFTR) had *pancreas divisum*. Two of those patients underwent an ERCP, and one of them developed post-ERCP pancreatitis

4. Discussion

In this study we evaluated the natural history of IRAP, a small subgroup of all patients who have recurrent acute pancreatitis. Idiopathic pancreatitis was reported frequently in the 1990s (10–30% of all patients with acute pancreatitis) but is becoming less common as our diagnostic tools are refined and we recognize the contribution of drugs, genetic mutations, and undiagnosed choledocholithiasis as causative mechanisms. [1,6] While previous studies have focused on measuring the recurrence rates of idiopathic pancreatitis after an initial episode, this is the first study evaluating IRAP after a second episode following strict diagnostic criteria. [7,8,13] In this retrospective review of 20 years of practice at three referral academic centers, we were able to identify only 35

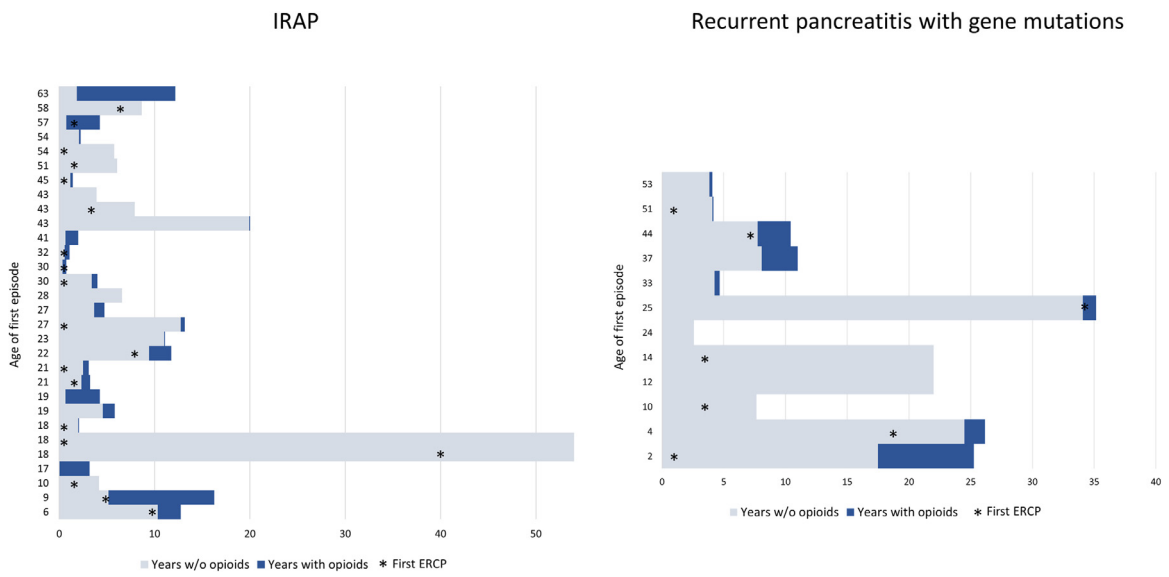

Fig. 3. Opioid and ERCP utilization among patients with IRAP and recognized genetic mutations.
Footnote: Time begins at first acute pancreatitis episode. Four patients removed for incomplete information: 2 incomplete details on opioid use, 2 unavailable date of first acute pancreatitis.

patients with true IRAP. Removing all patients with marginal alcohol use, patients who stopped having pancreatitis after a cholecystectomy, and genetic mutation carriers, this group was significantly small (only 27.3% of the "presumed IRAP" group). Four key findings stand out in this cohort.

First, the incidence of chronic pancreatitis is substantial in both IRAP patients and patients with recurrent acute pancreatitis and genetic mutations. Both groups developed chronic pancreatitis more frequently than patients with recurrent pancreatitis from alcohol or gallstone disease (38% after two pancreatitis attack, over 2 years of follow-up) and previous published series of IRAP (16.9% over 6.5 years follow-up). [4,14] Patients with IRAP and CFTR mutation carriers have a similar clinical course. Both had late onset of their first acute pancreatitis episode but progressed faster towards chronic pancreatitis. Patients with a SPINK1 mutation had their first episode of pancreatitis earlier in their lives but had a later diagnosis of chronic pancreatitis. The natural history of IRAP seems to support the SAPE hypothesis in which a sentinel injury occurs in different moments of life (ages ranging from 6 to 63 years) on a patient with impaired regenerative mechanisms. [9]

A second observation is that despite multiple hospital visits and poor quality of life, we were unable to identify a significant association with pancreatitis-related mortality or pancreatic cancer. This piece of information can be particularly useful in educating patients diagnosed with IRAP. Providers should acknowledge that IRAP is a disabling condition leading to multiple hospitalizations, but available retrospective research has not shown any significant association with pancreas-related mortality. Of note, PRSS1 mutation carriers represent a different population. Patients with PRSS1 mutation have a disproportionate pancreatic cancer risk and mortality. Our study only included one patient in this category and inferences in that regard are limited.

Third, sphincterotomies and other endoscopic interventions were frequently performed in both patient cohorts. In 2015 a small study showed encouraging results in 12 children with hereditary pancreatitis who improved after endoscopic therapy or surgery using a step-up approach (mean follow-up 32 months). [15] However a year later, a larger multicenter study showed that endoscopic sphincterotomy does not improve the clinical course of IRAP (median follow-up 84 months). [16] Endoscopic interventions can precipitate a new episode of acute pancreatitis, often times requiring hospitalization. [2] Over a longer period, stenting the pancreatic duct can cause delayed symptomatic strictures, even when performed to prevent ERCP-induced pancreatitis. [17] If a sphincterotomy is to be performed, biliary sphincterotomy is better than a double sphincterotomy (combination of biliary and pancreatic sphincterotomy), and patients with baseline abnormal manometry are prone to have more recurrences. [14] There is debate of whether minor papilla sphincterotomy benefits patients with *pancreas divisum* (seen in 23.4% of our patients). A systematic review showed that patients with recurrent pancreatitis and *pancreas divisum* have a median clinical response rate of 76%. The benefits of minor sphincterotomy should be balanced against a 50% rate of ERCP-related pancreatitis seen in our patient population (66% in mutation carriers). Response rates are even lower in patients with chronic pancreatitis (42%) and chronic abdominal pain (33%). [18] The SHARP trial is an ongoing multi-center, single blinded study, randomizing patients to minor papilla sphincterotomy or sham intervention that will hopefully answer this question. [19]

Finally, opioid medications were frequently used in both groups, with only minor differences noted. A larger percentage of IRAP were prescribed opioids but their utilization covered a shorter period. This is likely attributed to patients with genetic mutations being diagnosed at an earlier age with higher exposure to medical treatment allowing more prescription of oral opioids.

Since the discovery of PRSS1 gene in 1996, genetic mutations have gained relevance as causative agents of recurrent pancreatitis. Currently twelve mutations are linked to the development of pancreatitis: CASR, CEL, CFTR, CLDN2-MORC4 locus, CPA1, CTRB1-CTRB2 locus, CTRC, PNLIP, PRSS1, SBDS, SPINK1, and TRPV6. [20,21] Our results support the hypothesis of a "double hit" needed to develop acute pancreatitis in SPINK1 mutation carriers. [22] For example one patient had synergistic effect of SPINK1 (N34S) and CFTR mutation. This has been previously described for patients with N34S and p.R117H mutations, respectively. [23] In this series a new combination of SPINK1 (N34S) mutation and CFTR p.K684Nfs*38 mutation was identified. We did not identify any CTRC mutation carriers in our patient population. Previous reports

support that CTRC variants increase the risk of chronic pancreatitis but do not cause recurrent episodes. [24]

The contribution of introns in the development of pancreatitis is less studied than the effect of specific gene mutations. Polymorphism of the polythymidine tract in intron 8 of the CFTR gene have been associated with chronic pancreatitis in patients from Japan, England and Brazil. [25–27] Drinkers who carry the 5T/7T genotype (seen in 9 [16.7%] patients here), have a greater risk of developing chronic pancreatitis. [26,27] Drinkers with the homozygous T11/T11 genotype appear to be protected. [28] Other studies failed to confirm these associations between intron 8 genotypes and alcohol susceptibility. [29] Two reports from Japan ($N=28$ and $N=1$) identified polymorphisms in intron 9 linked to pancreatic disease (a splice-affecting variant c.1210-12 T5 and substitution 1525-18 GtoA). [30,31]

The genetic panel used in this cohort, does not typically report silent mutations in the CTRC gene. The mutation c.180C>T (p.G60G) is the most frequent mutation in pancreatitis. This silent mutation has a prevalence of 15-20% in controls without pancreatitis. While the relevance of silent mutations like p.G60G and other epigenetic changes is still an area of ongoing research, we advocate for this mutation to be reported regularly in genetic panels.

The diagnosis of drug induced pancreatitis continues to be a challenge in clinical practice and research. We identified one potential case of drug-induced pancreatitis. This patient was diagnosed with propofol induced pancreatitis, but no rechallenge was performed. For similar cases we recommend adopting the Badalov probability ranking into clinical practice. [32] Propofol is considered a Class Ib medication with at least 10 cases reported and one patient with positive rechallenge. Hypertriglyceridemia is the most likely mechanism behind propofol-induced acute pancreatitis. [33]

4.1. Strengths and limitations

This is the first retrospective study using a strict criterion for IRAP requiring negative genetic testing and pancreatitis episodes developed after a cholecystectomy. Planning a prospective study with adequate power on this population is challenging, requires significant resources and collaboration among multiple referral centers. A multicenter registry was designed 12 years ago for this purpose, with results still pending. This illustrates the challenges to recruit this patient population. [2] Use of individual-level data allowed us to follow a very precise population, and have an accurate count of hospitalizations, opioid prescription and endoscopy utilization. Considering the small sample size, our findings should be confirmed by larger multicenter studies.

The finding of biliary sludge remains confusing in the treatment of recurrent acute pancreatitis. Even though all patients in the cohort had a cholecystectomy, biliary sludge and stones can develop in the bile ducts leading to additional episodes of pancreatitis. Eighteen patients lacked information on imaging looking for sludge or gallstones prior to cholecystectomy (abdominal US, EUS, ERCP or MRI). This mechanism seems to be a particularly important in patients with CFTR mutation, where the transmembrane receptor makes bile thicker. In these patients a second anatomic variant like *pancreas divisum* is needed to cause recurrent pancreatitis. [34]

Efforts were made to exclude all known causes of acute pancreatitis and follow the Dutch Study group criteria, and our exclusion criteria was strict towards alcohol use. However we allowed patients with tobacco (past use) and marijuana (past or present use). Both drugs have been associated with acute and chronic pancreatitis. [35]

Our results are subject to limitations inherent from retrospective research, including selection bias, confounding and differential losses to follow up. There is a subgroup of patients who present to the emergency room during an acute flare and have minimal follow-up. Reviewers were confident counting the number of acute pancreatitis episodes in only 20 (41.7%) of patients reviewed. Similarly, the diagnosis of chronic pancreatitis depends on having follow-up with a clinician and receiving abdominal imaging after the second hospitalization for acute pancreatitis. We assumed that patients who underwent genetic testing had longitudinal care to some extent. Fecal elastase is not routinely performed in our clinical practice and was only checked in 3 (8.6%) patients. Fecal elastase is only helpful in severe exocrine pancreatic insufficiency and is a poor test for early chronic pancreatitis. [36] We hypothesize that prospective studies of IRAP patients may reveal higher incidence of chronic pancreatitis and diagnosis at earlier stages.

4.2. Implications: The value of genetic testing in this population

There is debate on the clinical value and cost-effectiveness of genetic testing in patients with recurrent pancreatitis. Even though recommended by current guidelines, clinicians question whether the results will guide their treatment. We advocate to perform testing for two reasons:

- Results guide the treating gastroenterologist to recommend advanced therapies. Young patients with disabling recurrent acute pancreatitis or painful chronic pancreatitis due to PRSS1 mutation qualify for a total pancreatectomy and islet auto-transplantation. Patients with disabling symptoms and multiple SPINK1 mutations also benefit from pancreatectomy. [37] In addition, experts recommend avoiding unnecessary sphincterotomies in patients with the CFTR mutation. [38]
- IRAP patients and mutation carriers gain understanding of the natural course of their disease. Three pancreatitis susceptibility genes, PRSS1, CPA1 and CTRC, are associated with increased risk of pancreatic cancer. Carriers of these mutations should be followed according to the International Cancer of the Pancreas Screening (CAPS) Consortium recommendations. [39] They should be referred to genetic counseling to discuss testing of relatives and impact on future generations.

The diagnosis of IRAP reflects our limitations in understanding the mechanisms that cause acute pancreatitis, and the cascade of events that lead to inflammation in genetically predisposed subjects. Current commercial genetic panels only evaluate four out of the twelve known genes involved in pancreatitis. Further research should evaluate the clinical relevance of other genes and their interactions with concomitant gallstones and alcohol use.

5. Conclusion

Recurrent pancreatitis is frequently seen in clinical practice but “True IRAP” is relatively uncommon after completing conventional laboratories, imaging, cholecystectomy and genetic testing. A significant percentage of these patients will develop chronic pancreatitis. While important differences in age of onset and progression rates were observed between IRAP patients and those with relevant genetic mutations, we failed to identify a significant association with pancreatitis-related mortality or pancreatic cancer in either group. Efforts to understand the genetic contribution to IRAP, minimize opioid prescription and reduce unnecessary endoscopic interventions are encouraged.

Disclosures

Conflict of interest statement for the authors: JEC received a travel Grant by AbbVie, Inc. and minor food and beverage compensation from Boston Scientific, Cook Medical, Gilead Sciences, Salix Pharmaceuticals, and Olympus America. We do not have any financial potential conflicts of interest.

Acknowledgment

Authors would like to thank Heather Flynn Gilmer CG, Nicole Boczek PhD, Linda Hasadsri MD PhD and the Division of Laboratory Genetics and Genomics, Department of Laboratory Medicine and Pathology, Mayo Clinic for their continuous support.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.04.013.

References

[1] Guda NM, Trikudanathan G, Freeman ML. Idiopathic recurrent acute pancreatitis. Lancet Gastroenterol Hepatol 2018;3:720–8. doi:10.1016/S2468-1253(18)30211-5.
[2] Romagnuolo J, Guda NM, Freeman ML, et al. Preferred designs, outcomes, and analysis strategies for treatment trials in idiopathic recurrent acute pancreatitis. Gastrointest Endosc 2008;68:966–74. doi:10.1016/j.gie.2008.05.006.
[3] Machicado JD, Yadav D. Epidemiology of recurrent acute and chronic pancreatitis: similarities and differences. Dig Dis Sci 2017;62:1683–91. doi:10.1007/s10620-017-4510-5.
[4] Lankisch PG, Apte M, Banks PA. Acute pancreatitis. Lancet 2015:85–96. doi:10.1016/S0140-6736(14)60649-8.
[5] Wilcox CM, Seay T, Kim H, et al. Prospective endoscopic ultrasound-based approach to the evaluation of idiopathic pancreatitis: causes, response to therapy, and long-term outcome. Am J Gastroenterol 2016;111:1339–48. doi:10.1038/ajg.2016.240.
[6] Levy MJ, Geenen JE. Idiopathic acute recurrent pancreatitis. Am J Gastroenterol 2001;96:2540–55. doi:10.1111/j.1572-0241.2001.04098.x.
[7] Ahmed Ali U, Issa Y, Hagenaars JC, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. Clin Gastroenterol Hepatol 2016;14:738–46. doi:10.1016/j.cgh.2015.12.040.
[8] Cavestro GM, Leandro G, Di Leo M, et al. A single-centre prospective, cohort study of the natural history of acute pancreatitis. Dig Liver Dis 2015;47:205–10. doi:10.1016/j.dld.2014.11.003.
[9] Working Group IAP/APA Acute Pancreatitis GuidelinesIAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13. doi:10.1016/j.pan.2013.07.063.
[10] Whitcomb DC. Hereditary pancreatitis: New insights into acute and chronic pancreatitis. Gut 1999;45:317–22. doi:10.1136/gut.45.3.317.
[11] Umans DS, Hallensleben ND, Verdonk RC, et al. Recurrence of idiopathic acute pancreatitis after cholecystectomy: systematic review and meta-analysis. Br J Surg 2020;107:191–9. doi:10.1002/bjs.11429.
[12] von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453–7. doi:10.1016/S0140-6736(07)61602-X.
[13] Yadav D, O'Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. Am J Gastroenterol 2012;107:1096–103. doi:10.1038/ajg.2012.126.
[14] Coté GA, Imperiale TF, Schmidt SE, et al. Similar efficacies of biliary, with or without pancreatic, sphincterotomy in treatment of idiopathic recurrent acute pancreatitis. Gastroenterology 2012;143. doi:10.1053/j.gastro.2012.09.006.
[15] Kargl S, Kienbauer M, Duba HC, et al. Therapeutic step-up strategy for management of hereditary pancreatitis in children. J Pediatr Surg 2015;50:511–14. doi:10.1016/j.jpedsurg.2014.05.016.
[16] Das R, Clarke B, Tang G, et al. Endoscopic sphincterotomy (ES) may not alter the natural history of idiopathic recurrent acute pancreatitis (IRAP). Pancreatology 2016;16:770–7. doi:10.1016/j.pan.2016.07.009.
[17] Adachi K, Yamauchi H, Kida M, et al. Stent-induced symptomatic pancreatic duct stricture after endoscopic prophylactic pancreatic duct stent placement for the normal pancreas. Pancreatology 2019;19:665–71. doi:10.1016/j.pan.2019.06.014.
[18] Kanth R, Samji NS, Inaganti A, et al. Endotherapy in symptomatic pancreas divisum: a systematic review. Pancreatology 2014;14:244–50. doi:10.1016/j.pan.2014.05.796.
[19] Coté GA, Durkalski-Mauldin VL, Serrano J, et al. Sp H incterotomy for A cute R ecurrent pancreatitis randomized trial: rationale, methodology, and potential implications. Pancreas 2019;48:1061–7. doi:10.1097/MPA.0000000000001370.
[20] Sadiq N, Gillani SW, Al Saeedy D, et al. Clinical review of acute, recurrent, and chronic pancreatitis: Recent updates of 2013-2019 literature. J Pharm Bioallied Sci 2020;12:112–23. doi:10.4103/jpbs.JPBS_313_19.
[21] Whitcomb DC, Gorry MC, Preston RA, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet 1996;14:141–5. doi:10.1038/ng1096-141.
[22] Ellison MA, Spagnolo DM, Shelton C, et al. Complex genetics in pancreatitis: insights gained from a new candidate locus panel. Pancreas 2020;49:983–98. doi:10.1097/MPA.0000000000001612.
[23] Dike CR, Kao SC, Uc A. Progression from acute to chronic pancreatitis associated with CFTR and SPINK1 mutations. Pancreatology 2020;20:1019–20. doi:10.1016/j.pan.2020.05.012.
[24] LaRusch J, Lozano-Leon A, Stello K, et al. The common Chymotrypsinogen C (CTRC) variant G60G (C.180T) increases risk of chronic pancreatitis but not recurrent acute pancreatitis in a North American population. Clin Transl Gastroenterol 2015;6. doi:10.1038/ctg.2014.13.
[25] Kimura S, Okabayashi Y, Inushima K, et al. Polymorphism of cystic fibrosis gene in Japanese patients with chronic pancreatitis. Dig Dis Sci 2000;45:2007–12. doi:10.1023/A:1005500210281.
[26] Da Costa MZG, Guarita DR, Ono-Nita SK, et al. CFTR polymorphisms in patients with alcoholic chronic pancreatitis. Pancreatology 2009;9:173–81. doi:10.1159/000178889.
[27] Sharer N, Schwarz M, Malone G, et al. Mutations of the cystic fibrosis gene in patients with chronic pancreatitis. N Engl J Med 1998;339:645–52. doi:10.1056/NEJM199809033391001.
[28] Nakamura Y, Ohmori T, Ishikawa A, et al. Homozygous (TG)11 allele in intron 8 of the cystic fibrosis transmembrane conductance regulator (CFTR) gene has a protective role against bicarbonate decrease in pure pancreatic juice among Japanese male alcoholics. Intern Med 2004;43:1131–7. doi:10.2169/internalmedicine.43.1131.
[29] Haber PS, Norris MD, Apte MV, et al. Alcoholic pancreatitis and polymorphisms of the variable length polythymidine tract in the cystic fibrosis gene. Alcohol Clin Exp Res 1999;23:509–12. doi:10.1111/j.1530-0277.1999.tb04145.x.
[30] Iso M, Suzuki M, Yanagi K, et al. The CFTR gene variants in Japanese children with idiopathic pancreatitis. Hum Genome Var 2019;6. doi:10.1038/s41439-019-0049-7.
[31] Seki K, Abo W, Yamamoto Y, et al. Identification of novel mutations of the CFTR gene in a Japanese patient with cystic fibrosis. Tohoku J Exp Med 1999;187:323–8. doi:10.1620/tjem.187.323.
[32] Badalov N, Baradarian R, Iswara K, et al. Drug-induced acute pancreatitis: an evidence-based review. Clin Gastroenterol Hepatol 2007;5. doi:10.1016/j.cgh.2006.11.023.
[33] Simons-Linares RC, Elkhouly MA, Salazar MJ. Drug-induced acute pancreatitis in adults: an update. Pancreas 2019;48:1263–73. doi:10.1097/MPA.0000000000001428.
[34] Bertin C, Pelletier AL, Vullierme MP, et al. Pancreas divisum is not a cause of pancreatitis by itself but acts as a partner of genetic mutations. Am J Gastroenterol 2012;107:311–17. doi:10.1038/ajg.2011.424.
[35] Barkin JA, Nemeth Z, Saluja AK, et al. Cannabis-induced acute pancreatitis: a systematic review. Pancreas 2017;46:1035–8. doi:10.1097/MPA.0000000000000873.
[36] Lankisch PG, Schmidt I, König H, et al. Faecal elastase 1: not helpful in diagnosing chronic pancreatitis associated with mild to moderate exocrine pancreatic insufficiency. Gut 1998;42:551–4. doi:10.1136/gut.42.4.551.
[37] Bellin MD, Gelrud A, Arreaza-Rubin G, et al. Total pancreatectomy with islet autotransplantation summary of a national institute of diabetes and digestive and kidney diseases workshop. Pancreas 2014:1163–70. doi:10.1097/mpa.0000000000000236.
[38] Dimagno MJ, Dimagno EP. Editorial: Pancreas divisum does not cause pancreatitis, but associates with CFTR mutations. Am J Gastroenterol 2012;107:318–20. doi:10.1038/ajg.2011.430.
[39] Goggins M, Overbeek KA, Brand R, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations for the international cancer of the pancreas screening (CAPS) Consortium. Gut 2020;69. doi:10.1136/gutjnl-2019-319352corr1.