When and does pancreas divisum cause chronic pancreatitis?

Gregory A. Cote, MD, MS
Associate Professor of Medicine
Why has this been such a lingering controversy?

• Causation is difficult to “prove” for a disease with multiple mechanisms and causes
• Recurrent acute pancreatitis and chronic pancreatitis often overlap, and are grouped in the literature - along with chronic pain
• Research bias
  • Endoscopic studies unblinded, inconsistent definitions, short-term follow-up, lack of comparison groups
• Referral bias
  • Epidemiological studies lack longitudinal natural history cohorts
Hill’s criteria for causation

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Limitations in divisum/pancreatitis research</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Strength</td>
<td>Several potential confounding etiologic factors</td>
</tr>
<tr>
<td>2. Consistency</td>
<td>High baseline prevalence of divisum; divisum ≠ pancreatitis</td>
</tr>
<tr>
<td>3. Specificity</td>
<td>Does divisum cause RAP, CP, both, or neither?</td>
</tr>
<tr>
<td>4. Temporality</td>
<td>Onset of pancreatic disease often impossible to measure</td>
</tr>
<tr>
<td>5. Gradient</td>
<td>Incomplete vs. complete, other variants?</td>
</tr>
<tr>
<td>6. Plausibility</td>
<td>Can duct obstruction cause pancreatitis?</td>
</tr>
<tr>
<td>7. Coherence</td>
<td>Epidemiology and experimental evidence are too weak to be coherent</td>
</tr>
<tr>
<td>8. Experimental evidence</td>
<td>Can divisum be treated? How to define benefit of Rx?</td>
</tr>
<tr>
<td>9. Analogy</td>
<td>Easy to analogize (PD obstruction → more pancreatitis)</td>
</tr>
</tbody>
</table>

Table adapted from Rothman KJ, Epidemiology: An Introduction, 2002
What causal factors are strongly and consistently associated with pancreatitis?

Prevalence estimates in the U.S.

- U.S. population age 18 and over: 248 million
- U.S. population that smokes: 36.5 million
- Alcohol use disorders: 15.1 million
- Pancreas divisum: 19.5 million
- **Symptomatic chronic pancreatitis:** 100,000
If pancreas divisum is a risk factor for pancreatitis, shouldn’t it be overrepresented in cohort studies?

Controls
• ERCP series underestimate the baseline prevalence of pancreas divisum in the general population
  • Choledocholithiasis and obstructive jaundice skew these estimates

Pancreatitis
• Prevalence of divisum higher in ERCP cohorts vs. MRCP
  • False positive rate of MRCP?
  • Reporting bias of ERCP?

DiMagno MJ and DiMagno EP, Pancreas 2007
Pancreas divisum is overrepresented among patients with susceptibility mutations

<table>
<thead>
<tr>
<th></th>
<th>iRAP/CP (n=40)</th>
<th>CFTR+ (n=30)</th>
<th>EtOH AP/CP (n=29)</th>
<th>Controls (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at the time of MRCP, median (range)</td>
<td>47 (18-79)</td>
<td>38 (17-62)</td>
<td>48 (35-67)</td>
<td>50 (20-79)</td>
</tr>
<tr>
<td>Pancreas divisum (n, %)</td>
<td>2 (5%)</td>
<td>14 (47%)</td>
<td>2 (7%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Parenchymal CP, n (%)</td>
<td>13 (33%)</td>
<td>16 (53%)</td>
<td>22 (76%)</td>
<td>-</td>
</tr>
<tr>
<td>Ductal signs of CP, n (%)</td>
<td>10 (25%)</td>
<td>17 (57%)</td>
<td>20 (69%)</td>
<td>-</td>
</tr>
</tbody>
</table>

- Divisum also associated with mutations in *PRSS1* and *SPINK1*
- CFTR mutations included common (7) and atypical (13) variants, and those of unknown significance (10)

Bertin et al, Am J Gastro 2012
Does divisum increase susceptibility to RAP/CP in the setting of CFTR and other susceptibility mutations?

CF causes mucoid pancreatic juice → duct obstruction
• Does divisum protect against pancreas insufficiency but then later predispose to AP?

P=0.01 (any mutation vs. all others)
P=0.04 (high-risk mutation vs. all others)

Nicholson JA, Johnstone M, Greenhalf W., AJG 2012
Plausibility: PD obstruction leads to acute and chronic pancreatitis

Acute gallstone pancreatitis

Main duct calcification $\Rightarrow$ progressive atrophy of the obstructed pancreas

Experimental evidence: Can pancreas divisum be treated?
Does endoscopic treatment of pancreas divisum improve natural history?

Typical outcomes table from an ERCP cohort study

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Total</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic sphincterotomy</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Endoscopic snare only</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endoscopic intervention failed</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical sphincteroplasty</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>2</td>
<td>2</td>
<td>12</td>
</tr>
</tbody>
</table>

Russell RCG, Wong NW, Cotton PB Gut, 1980
Retrospective cohort study with telephone follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>ARP (n=62)</th>
<th>CP (n=22)</th>
<th>Pain alone (n=29)</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yr</td>
<td>48.4</td>
<td>53.3</td>
<td>45.4</td>
<td>48.6</td>
</tr>
<tr>
<td>Female</td>
<td>40 (65)</td>
<td>13 (59)</td>
<td>27 (93)</td>
<td>80 (71)</td>
</tr>
<tr>
<td>Median sx duration, range (mo)</td>
<td>12 (1-168)</td>
<td>27 (1-100)</td>
<td>24 (3-100)</td>
<td>24 (1-168)</td>
</tr>
</tbody>
</table>

Long-Term Clinical Outcomes After Endoscopic Minor Papilla Therapy in Symptomatic Patients With Pancreas Divisum.
Borak, Gregory; Romagnuolo, Joseph; MD, FRCPC; Alsolaiman, Mohammad; Holt, Edward; Cotton, Peter; MD, FRCS
The only randomized trial of “divisum treatment” to date

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Stent</th>
<th>No stent</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>0/10</td>
<td>7/9</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>1/10</td>
<td>6/9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Improvement &gt;50%</td>
<td>9/10</td>
<td>1/9</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

- Unblinded
- Mean follow-up 29 months (stent) and 32 months (no stent)
  - Range not provided
How can endoscopic Rx change the natural history?

• Future episodes of acute pancreatitis
  • Eliminate
  • Reduce the number/frequency of future episodes
  • Severity
    • Duration
    • Need for hospitalization

• Interval development of chronic pancreatitis
• Quality of life (pain)
Negatives of minor papillotomy

• Dorsal duct cannulation is an independent risk factor for PEP
  • Baseline risk (1.2%)
  • Cannulation (8.2%, p< 0.01)
  • Minor papillotomy (10.6%, p< 0.01)
• Independent predictors of PEP include:
  • Attempted dorsal duct cannulation, OR 7.5
  • Minor papillotomy, OR 1.6
• Must consider PEP in the outcome measure!
• Other complications
  • Stent-induced injuries to the pancreatic duct
  • Sphincter re-stenosis may become an aggravating factor

Moffatt DC, Cote GA, et al. GIE 2011
Does pancreas divisum cause pancreatitis?

1. Divisum is associated with susceptibility mutations
   - Do susceptibility mutations cause pancreas divisum?
2. Divisum “treatment” may be effective in either case, but definitive studies are lacking in either
SHARP

SpHincterotomy for Acute Recurrent Pancreatitis

What really matters is if treatment helps