Chronic Pancreatitis: 
New Insights in Etiology

Michelle A. Anderson, MD, MSc
Associate Professor of Medicine
University of Michigan Health System
Ann Arbor, MI

Etiologies of Chronic Pancreatitis in 2003

Etiologies of Chronic Pancreatitis in 2013

- Alcohol: 45%
- Idiopathic: 29%
- Obstructive: 9%
- Genetic: 9%
- Other: 7%

What happened?

- Etiologies Changed?
- Human genetic testing became accessible and affordable
- Imaging got better and abundant
- Multigroup Studies and Cooperative Groups got it together
- “World” got smaller and we understood more!
Epidemiology of the Disease

- Annual Incidence 5-12/100,000\(^1,2\)
- Prevalence ~50/100,000\(^1,2\)
- African-Americans – 2-3x RR\(^3\)
- Alcohol
  - Risk increases in dose-dependent manner
  - Need to consume ≥ 35 drinks/week\(^4\)
  - Risk of CP after AP related to etoh use after
  - We can make a difference as physicians

---


---

Focus

- Tobacco
- Genetics
- Autoimmune Pancreatitis
Understanding the Role of Tobacco Use in Chronic Pancreatitis

Contribution of Tobacco Use to CP Risk in US

- NAPS2 Cohort Study 2000-2006, CP=539 Controls 695
- 3 Groups: Etoh, Non Etoh, Idiopathic
- After controlling for age, gender, BMI and ETOH, ever smoking, current smoking and dose of tobacco use were independently associated with idiopathic CP.
- Attributable Risk = 25%!


% Positive Reply

Smoking Status

Controls  Idiopathic CP

Current

Ever
To Quit or Not to Quit Smoking

Not to Quit

- 166 patients Italian & Swiss
- Idiopathic CP, longitudinal 5+ years
- Smoking $\rightarrow$ HR 2.09 (95% CI 1.07-4.10) pancreas calcifications, in shorter interval as well as diabetes (HR 3.94; 95% CI 1.14-13.6)

To Quit

- 360 patients Verona, Italy
- Mixed etiology, inc etoh
- Compared to never-smokers, ex-smokers were no more likely to develop calcifications (OR 0.56, 95% CI 0.2-1.4) while those that did were [OR 1.95 for ½ ppd and 1.76 for ppd]

Smoking is Under-Recognized

- More than 2/3 of Patients in NAPS2 smoked, yet cited as risk < ½ time
- More likely to recognize if:
  - Alcohol etiology, current user, heavy user, longer duration of use
- Strength of association is independent of recognition and all co-variates

Yadav, et al. Pancreatology 2010

Genes in Chronic Pancreatitis: Can’t someone make this simple?
Genetic Causes of Chronic Pancreatitis

- **PRSS1**
  - Hereditary Pancreatitis
  - Gain of Fxn
  - AD w/ 80% penetrance; 40% CA Risk

- **CFTR – Cystic Fibrosis**
  - Mutations vary from pulmonary phenotype
  - Rx coming?

- **SPINK1**
  - Scavenger of Trypsin
  - Heterozygotes \(\rightarrow\) inc. risk but need 2nd “hit”
  - N34S variant (tropical pancreatitis)

- **CTRC**
  - Chymotrypsinogen C
  - 2nd line after SPINK1

- **CASR**
  - Calcium-sensing receptor
  - Expressed in acini and ductal cells
  - Mutations \(\rightarrow\) Activated Trypsin

**KEY** \(\rightarrow\) ALL Lead to Trypsin active where it shouldn’t be!!

Chronic Pancreatitis-associated Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome location</th>
<th>Encoded Protein</th>
<th>Normal Function</th>
<th>Mutation causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRSS1</td>
<td>7q35</td>
<td>Cationic Trypsinogen</td>
<td>Digests Protein</td>
<td>Gain in Fxn</td>
</tr>
<tr>
<td>SPINK1</td>
<td>5q32</td>
<td>Serine protease inhibitor Kazal type 1</td>
<td>Scavenges activated trypsin in panc</td>
<td>Loss of Fxn</td>
</tr>
<tr>
<td>CFTR</td>
<td>7q31.2</td>
<td>Cystic Fibrosis transmembrane conductance regulator</td>
<td>Dilutes and alkalinizes pancreatic secretions</td>
<td>Loss of Fxn</td>
</tr>
<tr>
<td>CTRC</td>
<td>1p36</td>
<td>Chymotrypsinogen C</td>
<td>Highly specific for digesting trypsin</td>
<td>Loss of Fxn</td>
</tr>
<tr>
<td>CASR</td>
<td>3q13.3</td>
<td>Calcium-sensing Receptor</td>
<td>Controls electrolyte movement across acini</td>
<td>Loss of Fxn</td>
</tr>
</tbody>
</table>
Testing

- Why test?
  - Provides answers, limits further testing
  - Personal Risk of Other Diseases: Cancer, Fertility, Pulmonary
  - Implications for patient & family: lifestyle and reproduction
- Who to test?
  - Patients with early-onset disease (< 30 years old)
  - Patients with family history of pancreatitis or multiple pancreas cancers
- How to test?
  - Refer to genetic certified counselors
  - Refer to tertiary center (any of NAPS2 centers)
  - Get educated, do send-out testing (see me after) and do counseling yourself

Autoimmune Pancreatitis: The One You Don’t Want to Miss!
Case Presentation

68 yo M presents w/ obstructive jaundice, epigastric pain.

PE: epigastric tender, jaundice, -HSM. Vitiligo.

Labs: Bili 9.2 mg/dL, Alk Phos 629 U/L, AST/ALT 105/145 U/L.

August 2012
ASSOCIATED RETROPERITONEAL FIBROSIS

After 4 weeks of Prednisone 40 mg/day
Autoimmune Pancreatitis

**Sx**
- Jaundice
- Mass
- Abd pain
- Pancreatitis
- Other organ involvement

**Dx**
- Serum IgG4*
- ANA
- Imaging
- Bx
- HISORt

**Rx**
- Prednisone 40 mg/day x 4-6 weeks
- Taper 5 mg/1-2 weeks
- Azathioprine for failures or relapse

*ULN=140. IgG4>280 mg/dL are 99% specific but only 53% sensitive for AIP (Ghazale, et al. AJG 2007)

---

Types of AIP

<table>
<thead>
<tr>
<th>Feature</th>
<th>Type I – LPSP</th>
<th>Type II – IDCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60 ± 15 years</td>
<td>48 ± 19 years</td>
</tr>
<tr>
<td>Elevated serum IgG4</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Other Organs Involved*</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>IBD-associated</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Relapse Common</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

LPSP – lymphoplasmocytic sclerosing pancreatitis, IDCP – idiopathic ductocentric pancreatitis. * Other organs: Biliary, retroperitoneal, renal or salivary.

Pearls

- Encourage smoking cessation in all patients with acute pancreatitis who smoke as this increases the risk for recurrent attacks and CP
- Consider genetic causes in young patients or those with a family history of pancreatitis
- AIP is treatable. Knowing how to recognize it may save your patient!

Thank You!