Functional Biliary Syndromes

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Outline

• General concepts
• Controversies in functional biliary pain syndromes
  – Biliary dyskinesia
  – Sphincter of Oddi Dysfunction
• Understanding the nature of biliary pain
• Unifying concepts

Functional Biliary Syndromes

GENERAL CONCEPTS
Right Upper Quadrant Pain

“Chronic right upper quadrant pain allows greater scope for diagnostic and therapeutic mismanagement than perhaps any other abdominal symptom”

Kingham and Dawson 1985

Functional Biliary Syndromes according to ROME

- Functional gallbladder syndrome  
  (*gallbladder dyskinesia*)

- Sphinicter of Oddi Dysfunction  
  (*sphinicter of Oddi dysfunction*)
Rome Criteria for Biliary Pain

Pain located in the epigastrium and/or right upper quadrant and all of the following:

1. Episodes lasting 30 minutes or longer
2. Recurrent symptoms occurring at different intervals (not daily)
3. The pain builds up to a steady level
4. The pain is moderate to severe enough to interrupt the patient's daily activities or lead to an emergency department visit
5. The pain is not relieved by bowel movements
6. The pain is not relieved by postural change
7. The pain is not relieved by antacids

Patterns of Visceral Pain
Where Does biliary Pain Localize?

- 56 post-cholecystectomy patients
- T-tube in place
- Foley inserted into bile duct and distended
- Pain location mapped

Br J Surg 1967;54:599-605

Functional Biliary Syndromes

GALLBLADDER DYSKINESIA
GBD is a major clinical problem

- About 1 million new cases of gallbladder disorder per year in the USA
  - 700,000 cholecystectomies
  - most common gastrointestinal disorder requiring hospitalization
  - Cost estimated to be about $5 billion per year
- 10-20% of the cholecystectomies for Gallbladder Dyskinesia and rising

Studying function and dysfunction

- Image gallbladder: scintigraphy (or ultrasound)
- Give contractile stimulus: CCK or CCK-analog (meal)
- Measure difference in volume (before-after)
- “Normal” ejection fractions: 37-81%
CCK-HIDA scan: How specific is it?

- Low ejection fractions in 15-25% of normal volunteers
- EF can be affected by
  - Hormone replacement therapy
  - Exercise
  - Hyperglycemia
  - PPIs!

Trial Design: General Principles

1 = Does intervention relieve pain?
2 = Does diagnostic test select patients who benefit from intervention?
Randomized Clinical Trial of Cholecystectomy in GBD

Suspected Gallbladder Pain

- Normal GBEF (>40%)
  - No CCx: 60, 1 = Does CCx relieve pain?
  - CCx: 14, 57%

- Abnormal Test (<40%)
  - No CCx: 10, 0%
  - CCx: 21, 91%

1 = Does CCx relieve pain?
2 = Does GBEF select patients who benefit from CCx?

CCK-HIDA scan: Does it predict response to cholecystectomy?

Abnormal EF

Normal EF

Does GBEF predict gallbladder pathology?

<table>
<thead>
<tr>
<th>GBEF &lt;40%</th>
<th>GBEF &gt;40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>93%</td>
<td>64%</td>
</tr>
<tr>
<td>Chronic cholecystitis</td>
<td>Chronic cholecystitis</td>
</tr>
<tr>
<td>7%</td>
<td>36%</td>
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</tbody>
</table>

Wall thickness (mm)

Yapp et al

Functional Biliary Syndromes

SPHINCTER OF ODDI DYSFUNCTION
### Sphincter of Oddi Dysfunction

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Incidence of SOD</th>
<th>Response to ES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SOM+</td>
</tr>
<tr>
<td>Type I</td>
<td>75-95%</td>
<td>90-95%</td>
</tr>
<tr>
<td>Type II</td>
<td>55-65%</td>
<td>85%</td>
</tr>
<tr>
<td>Type III</td>
<td>25-55%</td>
<td>?</td>
</tr>
</tbody>
</table>

Lehman and Sherman 2000

### Randomized Clinical Trial of Sphincterotomy for SOD

- **Sham ES**
  - 73 patients
  - Treatment success:
    - < 6 days of lost productivity at months 9 and 12
    - No second intervention
    - No narcotics for abdominal pain during months 10, 11, and 12
  - 37%*

- **ES**
  - 214 patients
  - 141 treatment successes
  - 23%

Cotton et al. JAMA 2014;311(20):2101-2109

1 = Does sphincterotomy relieve pain in general?

NO, may be worse off!
Randomized Clinical Trial of Sphincterotomy for SOD

Subgroup Analysis

Normal SOM

Sham ES

ES

48% 1

20%

Abnormal SOM

Sham ES

ES

33% 1

24%

2 = Does SOM select patients in whom sphincterotomy relieves pain?

Cotton et al. JAMA 2014;311(20):2101-2109

Randomized Clinical Trial of Sphincterotomy for SOD

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“Pain is real when you get other people to believe in it. If no one believes in it but you, your pain is madness or hysteria.”

Naomi Wolfe
Understanding pain signaling…

1. Signal Transduction
2. Conduction
3. Neurotransmitter Release

Dorsal Root Ganglion

TO HIGHER CENTERS

Visceral organs are difficult to distinguish as sensorineural units

Dorsal Root Ganglion

TO HIGHER CENTERS

Pancreatic label  Gastric label  Orali

Knowles and Aziz. PAIN; 2009: 191–209

Li... Pasricha. Am J Physiol Gastrointest Liver Physiol; 2013 304:G490-500.
Clinical Implications

- 22 consecutive patients with severe chronic RUQ pain
- Average work-up:
  - 3.5 consultations
  - 7.3 procedures
  - 1.7 operations
  - >20 blood tests

Kingham and Dawson Gut 1985;26:783-788

Nociceptive Sensitization and Pain

Pasricha, Yamada Textbook of Gastroenterology
Evidence for a sensory disorder

Response to duodenal distension

Response to rectal distension

Desautels et al. Gastroenterology 1999

"Pain is real when you get other people to believe in it. If no one believes in it but you, your pain is madness or hysteria."

Naomi Wolfe

UNIFYING CONCEPTS

Functional Biliary Syndromes
Pathogenesis of Pain in Biliary Dyskinesia

- **Stasis**
  - Decreased activity of motor neurons

- **Inflammation**
  - PGE2
  - Increased sphincter contractility
  - Increased activity of sensory neurons (sensitization)

- **Distention**
  - Pain

References:
- Meg et al. J Gastrointest Surg 2002; 6:432
Pathogenesis of Post-Cholecystectomy Pain

- **Biliary dyskinesia**
- **Inflammation**
- **Nociceptive sensitization of the duodenobiliary-pancreatic region**

Cholecystectomy

- Sensitization persists → Persistent pain
- Sensitization resolves → Pain-free

Interruption of neural reflexes

Changes in SO pressure and dynamics → “SO Dysfunction”

Summary

- **GBD**
  - Possibly an inflammatory disorder
  - CCx is probably beneficial
  - The value of scintigraphy over clinical judgment in recommending CCx remains to be proven
Summary

• SOD
  – No evidence base to support utility of SOM or sphincterotomy in patients presenting with pain only
  – High complication rate and degree of difficulty makes it unacceptable for widespread use
  – Obsession with implicating sphincter has distracted us from looking at other contributing factors and therapies

Summary and Conclusions

• Visceral including biliary pain is a complex clinical and pathophysiological phenomenon
• Clinical criteria do not reliably indicate the true site of origin of pain because of overlapping neuroanatomical paths
• Sensitization of nociceptive nerves is a key factor in the generation of pain
So, so you think you can tell
Heaven from Hell,
blue skies from pain