Pain in diverticular disease

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Nottingham

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Pain in diverticular disease

Overview

- Incidence
- Patterns of pain
- Causes of pain
- Evidence of visceral hypersensitivity
- Impact of acute inflammation
  - Evidence from animal models
  - Human evidence
- Implications for treatment
Incidence

- 35% of >50 year old have diverticulosis in UK
- Onset of painful DD at mean age 55 years was 1.8/1000 patient years (6% over next 30 years)
  - Health Care Professionals Study Aldoori et al Am J Clin Nutr 1994;60:757-64
Who gets pain in diverticulosis?
Who gets pain in diverticulosis?

- 839 barium enema examinations
- 411 (53%) with diverticulosis
- Age: 69 (36-91) years median, range
- Gender: F/M 144 / 117
- Postal bowel symptom questionnaire
- 261/378 replied (69%)
Symptoms & Indications for barium enema

% reporting recurrent abdominal pain

Conclude approximately 85% are asymptomatic

Indications

- Change in bowel habit
- PR bleeding
- Misc
- Anaemia
- Cancer screening
Patterns of abdominal pain in diverticulosis

- 94 had recurrent short lived “IBS type” pain

- Frequency
  - 5[2-13] days/ month (median, interquartile range)

- Duration
  - 3(0.1-12 hour)
## Bowel symptoms in painful diverticulosis

94 patients with recurrent pain

<table>
<thead>
<tr>
<th>Symptom</th>
<th>n (%)</th>
<th>Frequency days / week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loose stool</td>
<td>50 (53.2)</td>
<td>5(1-7)</td>
</tr>
<tr>
<td>Hard stool</td>
<td>50 (53.2)</td>
<td>2(1-7)</td>
</tr>
<tr>
<td>Straining</td>
<td>41 (43.6)</td>
<td>3(1-7)</td>
</tr>
<tr>
<td>Urgency</td>
<td>45 (47.9)</td>
<td>3(1-7)</td>
</tr>
<tr>
<td>Incontinence</td>
<td>16 (17.0)</td>
<td>3(1-7)</td>
</tr>
<tr>
<td>Mucus per rectum</td>
<td>20 (21.3)</td>
<td>2(1-7)</td>
</tr>
<tr>
<td>Bloating</td>
<td>55 (58.5)</td>
<td>3(1-7)</td>
</tr>
</tbody>
</table>

Risk factors for chronic recurrent abdominal pain in diverticulosis

- Age
- Gender
- Severity of radiological appearance
- Bowel habit
Risk factors for chronic recurrent abdominal pain in diverticulosis

History of acute diverticulitis

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective</td>
<td>51</td>
<td>210</td>
</tr>
<tr>
<td>Community survey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged pain &gt;24 hours</td>
<td>31</td>
<td>137</td>
</tr>
<tr>
<td>Duration [median (range)] = 3(2-5) IQRdays</td>
<td>20</td>
<td>63</td>
</tr>
<tr>
<td>33/51 had medical attention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25/50 consultations → antibiotics</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p<0.0001 RR 2.0

Recurrent pain following acute diverticulitis

- Prospective study
  - 24 months follow up after hospitalisation with acute diverticulitis
    - Fever, WBC↑, abdominal tenderness with guarding
  - 18/26 patients experienced new recurrent short lived pain

CONCLUSION
Episodes of diverticular inflammation increase the risk of prolonged recurrent pain
Causes of pain?

• Increased wall tension
  – Distension
  – High amplitude Contractions

• Sensitisation by inflammation
  – Pain induced by normal pressure contractions
  – Spontaneous pain
Association between symptoms & postprandial contractions

- 30 healthy volunteers
- 115 patients with colonic diverticula
  - 30 asymptomatic (ADD)
  - 30 symptomatic uncomplicated (SUDD)
  - 55 symptomatic complicated (SCDD)

Temporal association of pain & contractions

- 12 patients with symptomatic uncomplicated DD
- 20 healthy controls
- 24 h L colon manometry
- Regular 2-3 cps activity as % of all activity
  - Control 6.4%
  - DD 31%
- Amplitude of contractions similar
  - Controls 25±9 mmHg
  - DD 29±11 mmHg

Temporal association of pain & contractions
Symptom associated probability (SAP)

For each individual divide record into 5 minute epochs
Record presence of pain or regular contractions

<table>
<thead>
<tr>
<th>Pain</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>No</td>
<td>C</td>
<td>D</td>
</tr>
</tbody>
</table>

• Chi squared test
• Probability of association occurring by chance = p
• SAP = (1-p) × 100
• 4 patients, 0 controls experienced pain during study
• **SAP 97-99%**

Evidence of visceral hypersensitivity in painful diverticular disease

10 asymptomatic DD (ADD)
11 symptomatic uncomplicated DD (SUDD)
Visceral sensitivity assessed by barostat

Clemens et al Gut 2004;53:717-22
Inflammation leads to Visceral hypersensitivity
Evidence from animal models

<table>
<thead>
<tr>
<th>Model</th>
<th>Abnormal motility</th>
<th>↑SP/5HT</th>
<th>Nerve damage</th>
<th>↓ NorA/ACh release</th>
<th>Hypersensitivity to distension</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. spiralis</td>
<td>+</td>
<td>↑SP/5HT</td>
<td>?</td>
<td>↓ NorA/ACh</td>
<td>+</td>
</tr>
<tr>
<td>TNBS colitis</td>
<td>+</td>
<td>↑5HT</td>
<td>+</td>
<td>↓ NorA</td>
<td>+</td>
</tr>
<tr>
<td>DSS colitis</td>
<td>+</td>
<td>↑5HT</td>
<td>+</td>
<td>↓ NorA</td>
<td>+</td>
</tr>
</tbody>
</table>
Role of Nitric Oxide in dysmotility in diverticular disease?

• Animal data suggests selective damage to nitrergic neurones by inflammation?
  – DSS colitis
• Human data
  – Diverticular disease
Effect of intestinal inflammation on colonic nitrergic neurones

• DSS induced distal colitis in rats
  – Inhibited colonic transit
  – Reduced NOS activity
  – Reduced nitrergic neurones in myenteric plexus
  – Reduced relaxation induced by EFS under NANC conditions

Mizuta et al Gastroenterology 2000;118:714-23
Evidence of impaired nitrergic innervation in Diverticulosis

- 11 Sigmoid colons with diverticulosis
  - resected for either cancer or diverticular disease
  - Muscle contractions recorded in organ bath in response to electrical stimulation (EFS)

Evidence of impaired nitrergic innervation in Diverticulosis

% showing relaxation on EFS

L-arginine
Precursor of NO

L-NNA
NO synthase blocker

Study of mechanisms in diverticular disease

• Resected specimens from acute and chronic diverticulitis
• Findings
  – Muscular hypertrophy
  – Altered nerve structure
  – Altered neuropeptide expression
Circular muscle hypertrophy in acute diverticulitis (AD) & symptomatic complicated diverticular disease (SCDD)

Kruskal-Wallis

Simpson et al 2003
Mucosal nerves in diverticulitis

• Protein gene product 9.5 (PGP9.5)

• Neuropeptide K

Simpson et al 2003
Increased PGP9.5 staining in circular muscle in AD & SCDD

Kruskal-Wallis p<0.000

Control AD SCDD

% area staining PGP 9.5

Simpson et al 2003

Control AD CD

Simpson et al 2003
Myenteric Plexus Peptides

Median; Range; IQR % circular muscle stained

Simpson et al 2003

**Substance P**

- Control
- AD
- SCDD

**Neuropeptide K**

- Control
- AD
- SCDD

**Galanin**

- Control
- AD
- SCDD

**VIP**

- Control
- AD
- SCDD
Mucosal Plexus Peptides

SP Mucosa

Neuropeptide K

Galanin

VIP

Median; Range; IQR % lamina propria

Control CD

Simpson et al 2003

Control         SCDD

Control         SCDD

Control         SCDD

Control         SCDD
Increased expression of galanin & tachykinins in symptomatic diverticular disease

- Prospective study
- Detailed bowel symptom questionnaire
  - 17 symptomatic
  - 15 asymptomatic DD pts
- Unprepared flexible sigmoidoscopy
  - Mucosal biopsy peridiverticular & rectal
- Normal appearance on routine histology
- No evidence of inflammation

Simpson et al 2003
Neuropeptides in Diverticular disease

Summary

Submucosal and myenteric nerves show similar pattern

<table>
<thead>
<tr>
<th></th>
<th>Submucosal</th>
<th>Myenteric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance P</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Neurokinin A</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Galanin</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

Significance?

- **SP/ NKA** involved in motility, secretion & pain perception
- **NK2 antagonists** reduce inflammation induced pain
- **Galanin**
  - Marker of nerve injury
  - Mediates pain hypersensitivity
  - Stimulates intestinal secretion
Pain in Diverticular Disease

Summary

• Diverticulosis alone is largely asymptomatic
• Need to distinguish episodic prolonged pain of diverticulitis from recurrent, short-lived, non-inflammatory pain
• Symptomatic patients with diverticulosis show
  – ↑ Postprandial motility
  – ↑ Sensitivity to colorectal distension
• Episodes of acute diverticulitis
  – Increase risk of pain
  – Cause smooth muscle hypertrophy
  – Cause acute disruption followed by regeneration of mucosal nerves
• Symptomatic patients with diverticulosis show in both mucosa & muscle
  – ↑ Galanin
  – ↑ Tachykinins
Conclusions

• Alteration in ENS / spinal horn may partly explain persistent disordered sensory / motor function following resolution of acute diverticulitis

Implications for new approaches to treatment

• Anti-inflammatory strategies for reducing acute inflammation?
• Treatments for visceral hypersensitivity?
Thank you for listening

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Biotechnology Biological Sciences Research Council
Altered cholinergic / SP sensitivity as cause of hypermotility in diverticulosis

- Conflicting data
  - Hyper-responsiveness to carbachol in 10 patients versus 10 controls
  - Increased M3 receptor immunostaining
  - Unaltered responsiveness to carbachol but reduced responsiveness to SP in 11 patients & 23 controls
    - Liu et al *J Pharmacol Exp.Ther* 2002;302:627-35

NB
- Small numbers
- Patients poorly characterised
- Symptoms not recorded
PGP staining increased in mucosa in SCDD

% area staining
PGP 9.5

* Mann-Whitney
p<0.000

Simpson et al 2003
Disrupted motility in Trichinella infection

Bercik et al Gastroenterology 2004;127:179
Inflammation increases substance P in mucosa and myenteric plexus

De Giorgio et al.
Gut 2001;49 : 822
Hypersensitivity to carbachol after *Trichinella* infection

Vallance et al 1998

Post inflammatory muscular hypertrophy

? Denervation hypersensitivity
Inhibitory effect of IL-1β on sympathetic nerve function

- Myenteric plexus preparations preincubated with H$^3$-labelled noradrenaline
- incubated with hrIL-1 10ng/ml ± IL-1ra

Hurst & Collins 1993
Changes in nitrergic neurones in achalasia

- 6 patients with end stage achalasia undergoing Heller’s myotomy and fundoplication
- Controls: esophageal carcinoma undergoing resection
- Stained for inhibitory nitrergic neurones using NADPH-Diaphorase histochemistry
Role of circulating antibodies in achalasia?

Rat ileum myenteric plexus stained with
A neurofilament antibody & B sera from achalasic patient
staining both NF +ve (large arrow) & NF-ve (small arrows) neurones

Verne et al 1997
Postinflammatory sensory / motor dysfunction

- Trichinella spiralis infected mouse
  - Acute inflammation followed by worm expulsion around day 14
  - Circular muscle hypertrophy associated with dysmotility
  - Increased sensitivity to cholinergic stimuli
  - Visceral hypersensitivity to distension
Abnormal motility after *T. spiralis* infection

**Duodenal manometry**

- *T. spiralis* infection in dogs inhibits normal mixing & enhances GMCs
  Sarna et al Gastroenterology 1991;101:664
- Stimulates clustered contractions, increases response to CCK
  Torrents et al Dig.Dis.Sci 2003;48:1035

Torrents et al Dig.Dis.Sci 2003;48:1035