Diverticular Disease and IBS: overlapping or misunderstanding?

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• Simple categorisation IBS or Diverticular disease? loses much information
• Heterogeneity in both groups
• Emphasis on understanding underlying mechanisms in each individual to facilitate “personalised medicine”
Overview

- Simple categorisation IBS or Diverticular disease? loses much information
- Heterogeneity in both groups
- Emphasis on understanding underlying mechanisms in each individual to facilitate “personalised medicine”

- What is the link between IBS and Diverticulosis?
- Mechanism of symptoms of IBS and symptomatic diverticular disease
- Role of Somatisation
- Practical aids to diagnosis
Differing effect of age and gender on risk of developing IBS and Diverticulosis

New diagnosis of IBS

Development of diverticulosis

1827 IBS & 3654 controls in Primary Care


1712 patients who had undergone colon testing

Jung et al. Am J Gastroenterol 2010;105:652-661
Association between IBS & Diverticulosis

Patient 1: IBS symptoms
Patient 2: Asymptomatic Diverticulosis
Patient 3: IBS-like symptoms

Population aged 65

- Life long IBS 10%
- Diverticulosis 40%
- Symptomatic DD

IBS with Diverticulosis
Asymptomatic Diverticulosis
Symptomatic DD
Association between IBS & Diverticulosis?

Cross sectional community survey in Olmsted county, Minnesota of patients who had had colonic imaging

Age 65 ±11 years

If have diverticulosis RR of IBS = 1.4 versus if have no diverticulosis

Jung et al  Am J Gastroenterol 2010;105:652-661
Association between IBS symptoms & Site of Diverticulosis in Asia

1009 Japanese patients undergoing screening colonoscopy

Age 64 ±13 years

Multivariate analysis
Odds ratio (95%CI)
Right sided 0.9(0.5-1.9)
Bilateral    2.6(1.3-5.2)
Left sided  3.1(1.4-7.1)
Mental component score <50  3.7(2.0-6.9)

Yamada et al  *Am J Gastroenterol* 2014;109(12):1900-5
Focus on role of left colon

• Huge natural experiment occurring in Japan with westernisation of diet and life style

• Shift in site of diverticulosis from right to left with associated increase in IBS-like symptoms

• Sigmoid colon commonest site for diverticulosis in Western populations

• Site of maximum colonic activity which postprandially is mostly retrograde
New insights into colonic response to eating from high resolution manometry

- Eating stimulates colonic motility
- Gradient of activity Sigmoid > Descending > Proximal colon motility
- >90% of increase motility is due to Retrograde cyclic contractions
- “Sigmoid braking mechanism”

Dinning et al Neurogastroenterol Motil 2014;26:1443-57
Causes of pain?

• Increased wall tension
  – Distension
  – High Amplitude Propagated Contractions

• Sensitisation by inflammation
  – Pain induced by normal pressure contractions

• Combination of abnormal motility and hypersensitivity
Increased postprandial contractions in symptomatic diverticular disease

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

Temporal association of pain with contractions

- 12 patients with symptomatic uncomplicated DD
- 20 healthy controls
- 24 h L colon manometry
- Amplitude of contractions similar
  - Controls 25±9 mmHg
  - DD 29±11 mmHg
- % time with regular contractions N sig different

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 = \( p \)
- \( SAP = (1-p) \times 100 \)
- 4 patients, 0 controls experienced pain during study
- SAP 97-99%

Why did controls not experience pain during similar contractions?

Clinical features of IBS versus SUDD
378 patients with diverticulosis surveyed, 261 replied
94 (36%) had recurrent abdominal pain

<table>
<thead>
<tr>
<th>Symptom</th>
<th>n (%)</th>
<th>Frequency days / week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloating</td>
<td>55 (58.5)</td>
<td>3(1-7)</td>
</tr>
<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>Urgency</td>
<td>45 (47.9)</td>
<td>3(1-7)</td>
</tr>
<tr>
<td>Straining</td>
<td>41 (43.6)</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>PR bleeding</td>
<td>27 (28.7)</td>
<td>2(1-7)</td>
</tr>
<tr>
<td>Incontinence</td>
<td>16 (17.0)</td>
<td>3(1-7)</td>
</tr>
</tbody>
</table>

Simpson et al
Location of pain in IBS & SDD

IBS
Generalised
Central
Vague descriptors
Typical visceral pattern

Diverticulitis
Lateralised
Localised
Usually Left iliac fossa
Somatic pattern
Patterns of pain in Acute Diverticulitis

Pain of diverticulitis: periodicity months or years
**Similar patterns of pain in IBS & SUDD**

IBS-type pain: recurrent, short lived, exacerbations lasting 2-3 days

![Graph showing pain patterns over days]

<table>
<thead>
<tr>
<th></th>
<th>IBS</th>
<th>SDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Frequency</td>
<td>12 (4-28) days /month(^1)</td>
<td>5(2-13) days/ month(^3)</td>
</tr>
<tr>
<td>Pain Duration</td>
<td>1-12 hours(^2)</td>
<td>3(0.1-12) hours(^3)</td>
</tr>
</tbody>
</table>

\(^1\) Spiller et al. Aliment Pharmacol Ther 2010;32:811-820
\(^2\) Weinland et al. Am J Gastroenterol 2011
## Similarities in known risk factors for developing IBS & SDD

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>IBS Odds Ratio (95% CI)</th>
<th>SDD Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Gender</td>
<td>1.6 (0.9, 2.6)</td>
<td>1.5 (1.5, 1.5)</td>
</tr>
<tr>
<td>Severe Anxiety</td>
<td>16.9 (6.7-42.6)</td>
<td>2.5 (1.1, 5.9)</td>
</tr>
<tr>
<td>High levels of illness behaviour/Moderate Somatisation</td>
<td>5.2 (2.5, 11.0)</td>
<td>4.1 (1.2, 13.5)</td>
</tr>
<tr>
<td>Fibre intake highest v lowest quintile</td>
<td>?</td>
<td>0.58 (0.4, 0.8)</td>
</tr>
<tr>
<td>BMI &gt; 30 kg/m</td>
<td>1.35 (1.1-1.7)</td>
<td>1.8 (1.1, 2.9)</td>
</tr>
<tr>
<td>Infection / Diverticulitis</td>
<td>7.3 (4.8-11.1)</td>
<td>4.7 (1.6, 14.0)</td>
</tr>
</tbody>
</table>

Link between bowel inflammation and visceral fat in DD

- Prospective cross-sectional study of 55 patients with diverticulosis
- 17 painless, 38 with recurrent abdominal pain
- Fat compartments measured using mDIXON MRI technique

![Adiponectin vs. Calprotectin](image1)

\[ r = -0.4, \quad P = 0.009 \]

![VAT vs. Calprotectin](image2)

\[ r = 0.3, \quad P = 0.048 \]

Murray et al. unpublished
Effect of acute diverticulitis

- Inflammatory damage to enteric nerves
- Altered neuropeptides
- Visceral hypersensitivity
- Disease anxiety
Mechanism of Visceral hypersensitivity in SUDD?

- 13 asymptomatic DD (ADD)
- 12 symptomatic uncomplicated DD (SUDD)
- Visceral sensitivity of rectum assessed by barostat
- mRNA for NK1 and TNFα measured in rectal biopsy

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Estimated odds ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M)</td>
<td>0.84 (0.37, 1.90)</td>
<td>0.677</td>
</tr>
<tr>
<td>Age</td>
<td>1.04 (0.99, 1.08)</td>
<td>0.129</td>
</tr>
<tr>
<td>Acute diverticulitis</td>
<td>3.98 (1.39, 11.36)</td>
<td>0.010</td>
</tr>
<tr>
<td>Anxiety score &gt; 7 on HADS</td>
<td>2.53 (1.09, 5.86)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

### Effect of somatisation

<table>
<thead>
<tr>
<th>PHQ-15</th>
<th>p-value</th>
<th>Estimated Odds ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0.68</td>
<td>1.24</td>
<td>0.45-3.43</td>
</tr>
<tr>
<td>Medium</td>
<td>0.02</td>
<td>4.09</td>
<td>1.24-13.51</td>
</tr>
<tr>
<td>High</td>
<td>0.002</td>
<td>33.43</td>
<td>3.60-310</td>
</tr>
</tbody>
</table>

During the past 4 weeks, how much have you been bothered by any of the following problems?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Not Bothered at all</th>
<th>Bothered a little</th>
<th>Bothered a lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach pain</td>
<td></td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Back pain</td>
<td></td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Pain in your arms, legs, or joints (knees, hips, etc)</td>
<td></td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Menstrual cramps or other problems with your periods (Women only)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headaches</td>
<td></td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Chest pain</td>
<td></td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
<td>✔</td>
</tr>
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<th>Not Bothered at all</th>
<th>Bothered a little</th>
<th>Bothered a lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fainting spells</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling your heart pound or race</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain or problems during sexual intercourse</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation, loose bowels, or diarrhoea</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Nausea, gas, or indigestion</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling tired or having low energy</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Trouble sleeping</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
Somatisation in IBS & Symptomatic Diverticular Disease

Role of somatisation

Marker of hypersensitivity or response to chronic pain?

Spiller et al Aliment Pharmacol Ther 2010;32:811-820
Mechanism of somatisation

• Abnormal CNS pain processing
• Common theme in
  – Fibromyalgia
  – Tempepo-mandibular joint dysfunction
  – Functional dyspepsia
  – Functional heartburn
  – IBS
• May be cause or effect!
Role of descending antinociceptive pathways

- ACC: Anticipation of pain, unpleasantness
- Insular: Second order appraisals, Prefrontal cortex
- AMYG: Arousal, autonomic response
- PAG: Descending antinociceptive pathways
- Spinal cord: 2nd order sensory neurone
Evidence for defective anti-nociception in IBS & subgroup of SUDD

• fMRI studies in IBS show impaired descending inhibition in anticipation of painful stimulus
• SUDD with somatisation show similar abnormal pattern of brain activation in anticipation of cutaneous thermal pain
  – Smith al et Neurogastroenterol Mot 2012;24:188
SUDD with Low PHQ12 deactivate amygdala > High PHQ12 with SUDD

Activations and Deactivations: [2 Sample t-test, Uncorr. P<0.05 threshold 5)

Cingulate Cortex
Left ACC
Left PFC
Right Amygdala

14 ADD, 14 SDD with PHQ12-SS>6, 14 SDD with PHQ12-SS<6,
Anticipation of cutaneous thermal pain

Smith al et Neurogastroenterol Mot 2012;24:188
Central & peripheral factors in IBS & SUDD

Symptom anxiety, Hypervigilance
Impaired descending antinociception

IBS  DD

CENTRAL

SOMATISATION

PERIPHERAL

CDD=Complicated DD
SUDD=Symptomatic Uncomplicated DD
Impact of “IBS-like” symptoms on outcome from surgical resection for recurrent diverticulitis?

IBS features predict less good outcomes from resection
75 patients undergoing colonic resection for “recurrent diverticulitis or stricture”

<table>
<thead>
<tr>
<th>Symptoms prior to resection</th>
<th>Excellent/good outcome</th>
<th>Fair / poor outcome</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower abdominal pain + difficulties in emptying bowel</td>
<td>Yes 7 (50%)</td>
<td>7</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>No 43 (86%)</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

• IBS and Symptomatic Diverticular Disease (SDD) share many symptoms
• Some have similar mechanisms (post-inflammatory & low grade inflammation)
• Optimum management in both depends on detailed assessment of both gastrointestinal and psychological factors
• Beware SUDD with somatisation!
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Thank you for your attention

Any Questions?
Visceral hypersensitivity: A key feature in IBS & SDD

- 10 asymptomatic DD (ADD)
- 11 symptomatic uncomplicated DD (SUDD)
- 9 Healthy controls
- Visceral sensitivity of rectum & sigmoid assessed by barostat

Clemens et al Gut 2004;53:717-22
Development of depression following acute diverticulitis

- Mental sequela of acute diverticulitis


Depression/ mood disorder
**Association between IBS & Diverticulosis**

**IBS ↔ Diverticulosis**

- **Could IBS cause diverticulosis?**
  - Prospective colonoscopy study 8.8% of IBS had Diverticulosis versus 21% of non-IBS
  - IBS were younger
  - Logistic regression including age shows no difference

- **Could Diverticulosis cause IBS-like syndrome?**
  - Most asymptomatic
  - ~1 in 10 patients with Diverticulosis → diverticulitis
  - Diverticulitis → IBS-like symptoms
Role of calprotectin

32 HC, 16 IBS, 16 ADD, 16 SDD without complications, 16 acute diverticulitis

Tursi et al  Int J Colorectal Dis 2009;24:49-55