Post-Infectious Irritable Bowel Syndrome

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Pathogenesis of IBS

Enck P. Nat Rev Dis Primers 2016;2:16014
Post-Infectious Irritable Bowel Syndrome

- Stewart GT. *Post-dysenteric colitis.* BMJ 1950;1:405-9
- Chaudhary NA, Truelove SC. *The irritable colon syndrome.* Q J Med 1962;31:3-7-22
Post-Infectious Irritable Bowel Syndrome

- Altered bowel habit and abdominal discomfort that persist after acute enteric infection despite clearance of the inciting pathogen and recovery from the acute illness
Walkerton, Ontario

- Agricultural community
- Population ~5000
- 180km NW of Toronto
- Groundwater supply: 3 drilled wells with chlorination units
Figure 8: Modelled Farm Drainage
Walkerton, Ontario

The drainage path was created using a digital elevation model (DEM). It shows surface water run-off, assuming that water flows downward along the steepest slope available. The DEM has a 10 meter spatial resolution.
## Walkerton: May 2000

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported cases of acute GE</td>
<td>1346</td>
</tr>
<tr>
<td>Affected Walkerton residents</td>
<td>799</td>
</tr>
<tr>
<td>Field epidemiology estimate of acute GE</td>
<td>2321</td>
</tr>
<tr>
<td>Affected Walkerton residents</td>
<td>1286</td>
</tr>
<tr>
<td>Hospitalizations*</td>
<td>65</td>
</tr>
<tr>
<td>Documented hemolytic uremic syndrome+</td>
<td>27</td>
</tr>
<tr>
<td>Attributable deaths</td>
<td>6</td>
</tr>
</tbody>
</table>

* 55% age 0 to 8
+ 52% age 1 to 4

BGOS Health Unit Investigative Report
Walkerton Health Study

Funded by Ontario MOH and CCFC

Multidisciplinary team:
- Nephrology, ID (UWO)
- GI (McMaster)

Mission: study long-term health outcomes and facilitate local access to medical care

Longitudinal cohort study 2001-2008

Recruitment through local town hall meetings and advertisements

In-person annual standardized interviews and assessments

Total enrolment: N=4561
Incidence of IBS 2 Years After Acute Gastroenteritis in Walkerton Ontario

Study cohort at risk of PI-IBS (N=2069):
Permanent Walkerton adult resident
No prior IBS, IBD, celiac disease

“Self-Reported” GE:
Increased stool frequency in May 2000 (> 3 BM/d for ≥ 3d)

“Clinically Suspected” GE:
Positive stool culture OR
Healthcare contact for acute illness during outbreak OR
Report of acute illness to 2000 public health survey

Marshall JK. Gastroenterology 2006;131:445-50
IBS After Infectious Enteritis: Systematic Review and Meta-Analysis

Klem F. Gastroenterology 2017 [in press]

- 45 studies (N=21,421)
- Follow-up 3 months to 10 years
- Relative risk for IBS if infectious enteritis in last 12 months:
  - 4.2 (95% CI 3.1-5.7)
- Pooled PI-IBS prevalence
  - 10.1% (95% CI 7.2-14.1) at 12 months
  - 14.5% (95% CI 7.7-25.5) > 12 months
- Risk factors for PI-IBS:
  - Female: OR 2.2 (1.6-3.1)
  - Antibiotics: OR 1.7 (1.2-2.4)
  - Anxiety: OR 2.0 (1.3-2.9)
  - Depression: OR 1.5 (1.2-1.9)
  - Somatization: OR 4.1 (2.7-6.0)
  - Neuroticism: OR 3.3 (1.6-6.5)
  - Clinical indicators of enteritis severity
PI-IBS After Viral Gastroenteritis

A Risk Score for Post-Infectious Irritable Bowel Syndrome

Risk Score Ranges from 0 to 90:
Low (<42) = 10%, Intermediate (43-68) = 35%, High (>69) = 60%
Age under 60 = 6; female = 9; duration more than 7 days = 7; maximum stool frequency more than 6 = 6; bloody stool = 4; abdominal cramps = 32; fever = 5; weight loss over 10 pounds = 8; pre-morbid anxiety/depression = 1; post infectious anxiety/depression = 10

McMaster University
JKM 2017

Persistence of PI-IBS Symptoms
(among subjects with IBS in 2002/2003)

Stability of IBS Phenotype

Long-Term Clinical Course of Shigellosis: 10-Year Follow-Up Study

- Prospective cohort study of 2001 Shigella outbreak in Korea
- 124 hospital employees infected by Shigella sonnei due to contaminated cafeteria food
- 105 age- and gender-matched non-infected controls

<table>
<thead>
<tr>
<th>Survey time (yr)</th>
<th>Shigella-exposed group</th>
<th>Control group</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total No.</td>
<td>No. of IBS</td>
<td>Total No.</td>
</tr>
<tr>
<td>1st</td>
<td>87</td>
<td>12 (13.8%)</td>
<td>89</td>
</tr>
<tr>
<td>3rd</td>
<td>87</td>
<td>13 (14.9%)</td>
<td>89</td>
</tr>
<tr>
<td>5th</td>
<td>53</td>
<td>11 (20.8%)</td>
<td>49</td>
</tr>
<tr>
<td>8th</td>
<td>71</td>
<td>11 (15.4%)</td>
<td>65</td>
</tr>
<tr>
<td>10th</td>
<td>86</td>
<td>20 (23.3%)</td>
<td>76</td>
</tr>
</tbody>
</table>
Luminal and Mucosal Factors in the Pathogenesis of IBS

Barbara G. Gastroenterology 2016;150:1305-18
Increased Intestinal Permeability with IBS in Walkerton Ontario

% Lactulose-Mannitol Ratio > 0.020

P=0.007

N=86 N=132

## Genetic Associations with PI-IBS

<table>
<thead>
<tr>
<th>Gene ID</th>
<th>Gene Category</th>
<th>SNP ID</th>
<th>Associated Allele</th>
<th>Frequency Controls</th>
<th>Frequency Cases</th>
<th>Odds Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR9</td>
<td>Innate immunity</td>
<td>P545P rs352139</td>
<td>A</td>
<td>41%</td>
<td>48%</td>
<td>1.38 (1.10-1.73)</td>
<td>0.0059</td>
</tr>
<tr>
<td>TLR9</td>
<td>Innate immunity</td>
<td>-T1237C rs5743836</td>
<td>T</td>
<td>82%</td>
<td>87%</td>
<td>0.69 (0.50-0.95)</td>
<td>0.025</td>
</tr>
<tr>
<td>IL-6</td>
<td>Innate immunity</td>
<td>-G174C rs1800795</td>
<td>C</td>
<td>39%</td>
<td>44%</td>
<td>1.28 (1.01-1.64)</td>
<td>0.042</td>
</tr>
<tr>
<td>CDH1</td>
<td>Intestinal epithelial barrier</td>
<td>-C160A rs16260</td>
<td>A</td>
<td>26%</td>
<td>31%</td>
<td>1.26 (0.99-1.61)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

IL-6 and CDH1 associations stronger when analysis restricted to subjects with confirmed gastroenteritis exposure

Genetic Variants are Independent PI-IBS Risk Factors
Multiple Logistic Regression Controlling for Clinical Predictors

<table>
<thead>
<tr>
<th>Variables</th>
<th>Reference</th>
<th>( P ) value</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs5743836:T (TLR9)</td>
<td>C</td>
<td>.0168</td>
<td>1.536 (1.080–2.182)</td>
</tr>
<tr>
<td>rs2069861:T (IL6)</td>
<td>C</td>
<td>.0345</td>
<td>1.509 (1.031–2.209)</td>
</tr>
<tr>
<td>rs16260:A (CDH1)</td>
<td>C</td>
<td>.0143</td>
<td>1.398 (1.069–1.829)</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td>.0159</td>
<td>0.986 (0.975–0.997)</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>.0238</td>
<td>1.521 (1.057–2.187)</td>
</tr>
<tr>
<td>Features of acute enteric illness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of diarrhea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–3 d</td>
<td>0–1 d</td>
<td>.976</td>
<td>0.987 (0.428–2.275)</td>
</tr>
<tr>
<td>4–5 d</td>
<td>0–1 d</td>
<td>.363</td>
<td>1.484 (0.634–3.476)</td>
</tr>
<tr>
<td>6–7 d</td>
<td>0–1 d</td>
<td>.626</td>
<td>1.242 (0.519–2.977)</td>
</tr>
<tr>
<td>&gt;7 d</td>
<td>0–1 d</td>
<td>.136</td>
<td>1.855 (0.823–4.183)</td>
</tr>
<tr>
<td>Bloody stools</td>
<td>No</td>
<td>.00338</td>
<td>1.845 (1.225–2.779)</td>
</tr>
<tr>
<td>Abdominal cramps</td>
<td>No</td>
<td>.000745</td>
<td>7.754 (2.258–25.499)</td>
</tr>
<tr>
<td>Weight loss (&gt;10 lb)</td>
<td>No</td>
<td>.000921</td>
<td>2.064 (1.345–3.169)</td>
</tr>
</tbody>
</table>

Prevalence of Dyspepsia at 8 Years Using Rome II Definition (Short-Form Leeds Dyspepsia Questionnaire)

OR for dyspepsia at 8 years:
- Clinically confirmed vs. controls = 2.67 (1.80-3.95)
- Self-reported vs. controls = 2.38 (1.69-3.38)

Post-Infectious IBS After Long-Distance Travel

- Survey of 1190 long-distance travelers, 7 months after journey
  - Traveler’s diarrhea (at least moderate) in 43.3%
  - New-onset IBS at 7 months post travel in 7.2% (95% CI 5.8-8.6)
    (10.7% if diarrhea during travel vs. 2.5% if no traveler’s diarrhea)
Conclusions

• The Walkerton outbreak was an awful human tragedy
• The contributions of citizens of Walkerton have enhanced understanding of post-infectious IBS
• New insights:
  – Epidemiology and natural history
    • Adult
    • Adolescent
  – Risk factors and risk profiling
  – IBS phenotype stability
  – Risk of IBD
  – Role of intestinal permeability
  – Genetic risk factors
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