THE OVERLAP BETWEEN INFLAMMATORY BOWEL DISEASE AND FUNCTIONAL GASTROINTESTINAL DISORDERS: CHALLENGES AND TREATMENT IMPLICATIONS

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Nationwide Children’s Hospital

Weekly Prevalence of Symptoms USA vs. Colombia

<table>
<thead>
<tr>
<th></th>
<th>Colombia (n=245)</th>
<th>USA (hospital data) (n=207)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abdominal Pain</strong></td>
<td>28%</td>
<td>38%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>22%</td>
<td>22%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>11%</td>
<td>8%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>5%</td>
<td>9%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>7%</td>
<td>7%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Other Gastrointestinal Symptoms</strong></td>
<td>31%</td>
<td>42%</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Headaches</strong></td>
<td>39%</td>
<td>36%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Non Abdominal Pain</strong></td>
<td>29%</td>
<td>15%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Saps M, et al. NASPGHAN 2012

MOST CHILDREN CONSULTING FOR ABDOMINAL PAIN DO NOT HAVE AN ORGANIC CAUSE TO EXPLAIN THEIR PAIN

10% of children miss school for abdominal pain

Children with abdominal pain have worse quality of life and disabilities

Abdominal Pain

Pediatric Crohn's Disease Activity Index

Abdominal pain:
- None
- Mild: brief, does not interfere with activities
- Mod/severe: daily, longer lasting affects activities, nocturnal


Ulcerative Colitis - Inflammation lowers pain threshold to rectal distension


Frequency and Urgency in Ulcerative Colitis


Active disease
- Lower volume required to induce - desire to defecate and cause a sustained anal relaxation
- Maximum tolerable rectal volume lower in patients with active colitis

Remission of disease
- Decrease in rectal sensitivity
- Increase in rectal compliance

Hypersensitive and poorly compliant rectum

Viscoelastic Properties
- Edema related to inflammations may results in changes in viscoelastic properties of the gut.
- Stiffness in the gut will lead to increased resistance to the passage of feces and gas in the affected segment, proximal dilatation and pain and urgency.
Sensation

Inflammation may lead to a cascade of cellular and nervous mechanisms, possibly activating the nociceptive system independently of any mechanical changes.

Ulcerative colitis—inflammation lowers pain threshold to rectal distension

Colonic irritation in rats leads to visceral hypersensitivity


Gastrointestinal Transit
Sitz-Markers

Active Colitis

- Gastric emptying—similar
- Mouth-to-caecum transit - slower
- Rectosigmoid—rapid transit

Quiescent colitis

- Colonic distribution of markers was normal

Some IBD patients in clinical remission continue experiencing symptoms of pain despite resolving inflammation

- 30–50% of adult IBD patients in clinical remission (no inflammation) experience abdominal pain
- Up to one-sixth of IBD patients are chronically treated with opioids


- IBS-like symptoms among IBD patients in remission - 31.5% (UC), 41.7% (CD)


Prevalence of IBS-like symptoms among children with IBD
CD 6%
UC 14%


13% of children with IBD and abdominal pain have a functional disease


Overlap of functional abdominal pain in pediatric Crohn’s disease


- Prevalence of FAP in children with inactive IBD is lower than adults and closer to the prevalence of functional disorders in general population of children
- Abdominal pain predominant-functional gastrointestinal disorders - 11.8%

Colonic irritation in neonatal rats, leads to chronic visceral hypersensitivity, associated with central neuronal sensitization in the absence of peripheric pathology.


**Early Life Events as Predictors of Pediatric Chronic Abdominal Pain**


**Critical periods for neonatal insults to cause long-term changes to pain and somatosensation (rodents)**

\textbf{Sensation}

- Repetitive sigmoid stimulation - UC no fall in threshold
- IBS - Repetitive sigmoid stimulation reduced threshold for pain and falls even further
- Chronic inflammation \textit{alone} does not lead to visceral hypersensitivity
- Visceral hypersensitivity depends \textit{not only on} peripheral input \textit{but also on} descending influences (facilitatory and inhibitory)

\textbf{Barostat rectal testing in IBS}

\textbf{Inhibitory Pathway}

\textbf{Pain Gate}


Some IBD patients in clinical remission continue experiencing symptoms of pain despite resolving inflammation

- Sensory pathways sensitize during inflammation, leading to persistent changes in afferent neurons and central nervous system pain processing.
- Pain processing and activation of sensory pathways is modulated by arousal, emotion, and cognitive factors.


Differences in thickness between patients with chronic gut inflammation, functional GI disorders and healthy


- UC and IBS- lower cortical thickness in insula (different regions)
- UC- reduction certain areas (chronic inflammation driven afferent input)

Changes in somatosensory cortex in UC and IBS but degree did not correspond to pain reports (UC more changes and less pain than IBS)

Rectal Distension Induced Activations

Sood M et al. NASPGHAN 2014

IBS patients demonstrated significantly increased activation in:
- Anterior cingulate
- Insula
- Frontal cortex
Deactivation in sensory and motor areas
Health Quality of Life

- In IBD and IBS, psychological distress has a stronger direct effect on HRQOL than GI symptoms

- Psychological distress is less dependent on GI symptom severity in IBS compared with IBD

Persistent pain despite clinical remission

Biopsychosocial problem- Comorbidities including anxiety and depression in IBD patients have central modulating effects

IBS and IBD patients have negative correlations between:
1. Psychological symptoms and HRQOL
2. GI symptoms and HRQOL

Difference between IBS and IBD
- Greater association between GI symptoms and psychological distress in IBD
- Psychological distress less dependent on severity of GI symptoms in IBS than IBD

Psychological distress is related to worsening GI symptoms in IBD patients and therefore may improve with relief of GI symptoms


<table>
<thead>
<tr>
<th></th>
<th>Medical Therapy</th>
<th>Hypnotherapy</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Rectal sensitivity scores</td>
<td>15 mm Hg</td>
<td>19 mm Hg (P=0.09)</td>
</tr>
<tr>
<td>Patients with rectal hypersensitivity (N)</td>
<td>6/20 (P=0.07)</td>
<td>4/20 (P=0.04)</td>
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</table>

- Treatment outcomes: Although rectal hypersensitivity improved in hypnosis, rectal hypersensitivity did not correlate with outcome

- Conclusion: Clinical success with hypnotherapy not explained by improvement in rectal sensitivity.

Hypnosis

- State of deep relaxation
- Focused attention
- Teach patients to control symptoms and physiological functions not easily accessible to conscious manipulation

Ulcerative Colitis Hypnotherapy Trial

- Prevention of relapse
- Randomized clinical trial comparing 7 sessions of standardized gut-directed hypnotherapy (n=19) versus active attention (n=17)
- Improvement in the IBDQ bowel health subscale with the hypnosis at 20 weeks (p = .05).
- Hypnosis reported more improvement in physical quality of life over time at both posttreatment (p = .04) and 20 weeks (p = .03).

Predicting relapse in Crohn's disease


- Temporal relationship between psychological distress and acute stressors
- Stressors: Worsening of IBD symptoms and subsequently a disease flare.
- Patients under low stress and low on avoidant coping (social diversion or distraction) are less likely to relapse.

IBD – Anxiety- Depression

- 36 adolescents with IBD (ages 12-17)
- Clinical levels of anxiety (22%)
- Depressive symptoms (30%)
- Regression analyses - IBD-specific anxiety significantly associated with greater utilization of medical services and worsened psychosocial functioning.

**Adolescents with IBD**

- Adolescents with IBD (n=50), healthy (n=42)
- Higher risk for psychosocial difficulties than healthy adolescents
- IBD more anxious or depressed symptoms (p < .05) and social problems (p < .01)
- More adolescents with IBD (14%) - clinically significant social problems


**Children with CD and abdominal pain at risk of depression regardless of disease activity**

Proportion of patients with Crohn’s disease and functional abdominal pain with depressive symptoms compared to other Crohn’s disease patients.

**Parenting stress predicts depressive symptoms in adolescents with inflammatory bowel disease.**

- Baseline parenting stress accounts for a significant amount of the variance in depressive symptoms at follow-up (P<0.05).
- CONCLUSION: Parenting stress impacts adolescent depressive symptoms in IBD. Identification of parenting stress and adolescent depression should occur early and possibly in the context of routine clinic visits.
**Behavioral Self-Management Program**

- Comprehensive program to address stress and improve coping for the management of IBD (8 weeks)
- Techniques for stress management, and increased self-efficacy - disease/medication knowledge, coping and medication adherence
- Incidence of flare within 12 months following behavioral intervention compared to natural history of flare incidence prior to program participation

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<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>Increase</th>
<th>p</th>
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<tbody>
<tr>
<td>Treatment</td>
<td>13.1%</td>
<td>6.1%</td>
<td>57%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Control</td>
<td>10.2%</td>
<td>8.5%</td>
<td>18%</td>
<td>.4</td>
</tr>
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**IBD and anxiety**

- 9 children/adolescents with IBD and anxiety
- CBT program at GI’s office
- Pretreatment vs. post-treatment - 88% treatment responders, 50% no longer met criteria for their principal anxiety disorder
- Decreases in: anxiety, pain, disease severity


**Primary and Secondary Prevention**


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<tr>
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<td>NS</td>
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<tr>
<td>Severity</td>
<td>p&lt;.07</td>
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<tr>
<th>Headaches</th>
<th>Prevalence</th>
<th>p&lt;.04</th>
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<td>p&lt;.001</td>
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| Functioning    | p<.001     |       |
| Play           | p<.001     |       |
| Gymnastics     | p<.001     |       |
| Abstinence     | p<.03      |       |

Intervention group missed 1.3 less days of school control group (p=.01)

4% of children with abdominal pain seek medical attention

Abdominal Pain

Psychological Risk Factors

5 Year Longitudinal Study: Children with persistent abdominal pain > anxiety, depression and negative life events and lower self worth

Psychological Risk Factors

5 Year Longitudinal Study: Children with persistent abdominal pain > anxiety, depression and negative life events and lower self worth


The End