Chronic Abdominal Pain in the Pediatric Emergency Department

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Objectives

• Review Functional Gastrointestinal Disorders
• Discuss a defined criteria approach to diagnosis of Functional GI Disorders; as opposed to an approach to rule out organic disease
• Discuss role of lab and DI investigations for patients with chronic abdominal pain in the emergency department.

Outline

• Reasons for discussing Chronic Abdominal Pain
• Pathophysiology of chronic abdominal Pain
• Rome III criteria
• AAP technical report and guidelines from the subcommittee on Chronic Abdominal Pain
Chronic Abdominal Pain in Pediatric Emergency: Why talk about it?

- Prevalence: unknown but high
- ED numbers?
- Emergency Medicine approach – rule out organic disease (prove a negative)
  - Cases...

Case 1

- 14 yo female with several year history of recurrent abdominal pain, missing school, family worried “we are missing something”
- Multiple investigations including 5 abdominal ultrasounds one which eventually showed a dilated common bile duct. Had ERCP, normal exam but complicated by bleeding requiring ICU stay, transfusion and surgery.
- Presenting 6 months after with the same pain

Case 2

- 10 yo male sent to ED with appendicitis on US
- Hx – > 1 year of recurrent abdominal pain. Multiple investigations always normal, including lab and US in past.
- US done 2 days prior to presentation - ? Appendicitis recommend US follow-up
- Repeat US – same so to ED
- Exam benign, labs normal - now what?
Case 3

- 14 yo female with recurrent abdominal pain for 6 months
- Seen the previous night in our ED, exam benign, labs normal
- Discharged for US in am
- US unremarkable but can’t see appendix, family wonders if a CT might be better and requests GI referral – now what?

Definitions

- Recurrent Abdominal Pain (Apley and Naish 1950’s) - used to describe all abdominal pain without organic etiology
- Criteria: at least 3 bouts of pain, severe enough to affect activities over a period of at least 3 months
- Many terms used interchangeably
  - Chronic abdominal pain, functional abdominal pain, psychogenic abdominal pain

Vast Majority of these patients have Functional Pain but....

- Parents are very worried
- Child usually missing lots of school, complaining of severe discomfort
- Physicians worried about missing underlying occult disorder so keep ordering tests, reinforcing the concept that something is being missed
Pathophysiology of Functional Abdominal Pain

- Abnormalities in the Enteric Nervous System
  - Dysregulation of the brain-gut communication
- Dysmotility - no difference in patients with FGID and controls
- Current theory – abnormal bowel reactivity to
  - Physiologic stimuli - meals, gut distension, hormonal changes
  - Noxious stimuli – inflammatory (post infectious)
  - Psychological stimuli

Visceral Hyperalgesia, and Hypersensitivity

- Decrease pain threshold to changes in intraluminal pressure
- Altered cognitive sensation of normal regulatory gut action
- Useful when talking to families, can use the analogy of skin hypersensitivity post burn
Pathophysiology

- Ascending Visceral Pain transmission
- Descending Modulation of pain
- Visceral sensitization
  - Anatomic location of hypersensitization
  - Biochemical mechanism of hypersensitization
- Role of the CNS

Ascending Visceral Pain Transmission

- Ascending stimulus from colon ascends spinothalamic tract to:
  - Somatosensory cortex – localization and intensity of afferent signals
  - Limbic System specifically in the anterior cingulate cortex (ACC) = motivational-affective component
  - Insular Cortex – integrates visceral, sensory and emotional information
Ascending Visceral Pain Transmission

- Limbic System – modulator of pain experience based on emotional state, prior experience and cognitive interpretation
- These systems work in chronic pain by modulating the afferent sensory information from the gut allowing the perception of pain in the absence of noxious input.

Evidence

- PET scanning and radiolabeled oxygen studies
  - Hot Water immersion of hand patients hypnotized to experience pain or pleasure
    - Sensory cortical activity the same
    - Those who experienced pain had much greater activation of limbic system – affective component of pain experience
  - Visceral stimulation in patients with FGID’s vs controls showed similar differences in limbic system activity

Descending Modulation of Pain

- Gate control theory - descending inhibitory or endorphin-mediated analgesic system
- Inhibitory impulses work on dorsal horn neurons via release of serotonin to modulate afferent impulses
- Brain imaging studies demonstrate increased activity in midbrain structures during painful stimuli as this region activates endogenous opiates
Visceral sensitization
• Recurrent peripheral stimulation up-regulates afferent signals or inhibits descending pain control mechanisms, sensitizing the bowel and producing visceral hyperalgesia

Evidence for Visceral Hyperesthesia
• Healthy volunteers – repetitive balloon inflations in colon caused a transient increase in pain intensity and a 228% increase in the area pain was experienced
• Patients with FGID’s had greater degree on increased pain perception
• CNS response to peripheral injury can be modified by prior reduction of afferent input to spinal cord and CNS – pre-op pain treatment decreases post-op pain severity during recovery

Location of visceral hypersensitivity
• Mucosa – inflammation or tissue damage increases afferent nociceptors which increases response to afferent neurons. This can outlast the noxious stimulation (pain memory) so that normal regulatory stimuli are perceived as painful
• Spine – spinal hyperexcitability – up regulation of dorsal horn neurons in response to noxious stimulation (inflammation or trauma) persists causing increased perception of normal stimuli
Biochemical Mechanisms of Sensitization

• Serotonin is the primary neurotransmitter of the ENS, and mediates bowel contraction, relaxation, secretions and of pain and nausea via different receptor types and location
• Repeated stimulation at the level of the spinal cord causes release of stimulatory neuropeptides, excitatory amino acids and oncogene Fos which encodes neuropeptidesthesp dynorphin

Biochemical Mechanisms of Sensitization

• Increased dynorphin gene expression can increase neuronal excitability for days to weeks
• Animal studies show strong relationship among noxious stimuli-induced Fos protein expression, dorsal horn neuronal excitability and prolonged behavioral hyperalgesia
• New research is measuring these chemicals looking for a biomarker for FGID’s

Role of the CNS

• Life stress, anxiety disorders, maladaptive coping, are associated with FAPS and may impair descending inhibitory pathways or may amplify visceral afferent signals
Evidence

• Gwee, 1999
  – 94 patients admitted with gastroenteritis
  – 72 recovered, 22 had abdominal pain at 3 months
  – No difference in gut hypermotility or visceral sensitivity
  – Symptomatic group
    • Greater psychological distress at time of infection
    • More mucosal inflammatory cells at 3 month

Evidence

• PET and functional MRI studies show abnormal activation of the limbic system and thalamus in response to rectal dilatation in patients with IBS
• Treatment and resolution of pain and distress correspond with a return of limbic system function to normal
• Similar changes seen in the treatment of depression
• Dysregulation of central pain modulation may occur in various medical and psychological conditions and treatment may reverse this

Clinical
Positive diagnostic criteria
Rome III

• AAP and North American Society of Gastroenterology subcommittee on Chronic Abdominal Pain
  – Clinical report and clinical guidelines – Pediatrics 2005
  – Rome III criteria published in Gastroenterology 2006
• Attempt to apply evidence based medicine to Functional Gastrointestinal Disorders and to Validate their definitions
• GOAL – use defined criteria diagnosis of these disorders rather than an approach of excluding organic disease by means of investigations

Functional Gastrointestinal Disorders

**Table 1.** The Functional Gastrointestinal Disorders

<table>
<thead>
<tr>
<th>H. Functional disorders: children and adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1a. Vomiting and aerophagia</td>
</tr>
<tr>
<td>H1b. Oesophageal vomiting</td>
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<tr>
<td>H1c. Dysphagia</td>
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<tr>
<td>H2. Abdominal pain-related FGIDs</td>
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<tr>
<td>H2a. Functional dyspepsis</td>
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<tr>
<td>H2b. Irritable bowel syndrome</td>
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<tr>
<td>H2c. Abdominal migraine</td>
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<tr>
<td>H2d. Childhood functional abdominal pain syndrome</td>
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<tr>
<td>H3. Constipation and incontinence</td>
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<tr>
<td>H3a. Functional constipation</td>
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<tr>
<td>H3b. Neurogenic fecal incontinence</td>
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Abdominal Pain-Related FGIDs

**Rome III**

**Table 2.** Alarm Symptoms, Signs, and Features in Children and Adolescents With Nongynecologic Abdominal Pain–Related Functional Gastrointestinal Disorders

<table>
<thead>
<tr>
<th>Persistent right upper or right lower quadrant pain</th>
<th>Pain that wakes the child from sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphagia</td>
<td>Arthritis</td>
</tr>
<tr>
<td>Persistent vomiting</td>
<td>Perineal disease</td>
</tr>
<tr>
<td>Gastrointestinal blood loss</td>
<td>Involutary weight loss</td>
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<tr>
<td>Nocturnal diarrhea</td>
<td>Deceleration of linear growth</td>
</tr>
<tr>
<td>Family history of inflammatory bowel disease, celiac disease, or peptic ulcer disease</td>
<td>Delayed puberty, Unexplained fever</td>
</tr>
</tbody>
</table>
Functional Dyspepsia

H2a. Diagnostic Criteria* for Functional Dyspepsia

Must include all of the following:

1. Persistent or recurrent pain or discomfort centered in the upper abdomen (above the umbilicus)
2. Not relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not IBS)
3. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

*Criteria fulfilled at least once per week for at least 2 months before diagnosis

Functional Dyspepsia

- Prevalence 12-15% age 4-18 yo
- Previous definitions required endoscopic diagnosis, this was changed as likelihood of finding mucosal abnormality is very low
- May have onset post viral infection
- No definitive studies to support any treatment – antisecretory agents (H2 or proton pump inhibitors) or prokinetics

Irritable Bowel Syndrome

Must include all of the following:

1. Abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with 2 or more of the following at least 25% of the time:
   a. Improved with defecation
   b. Onset associated with a change in frequency of stool
   c. Onset associated with a change in form (appearance) of stool
2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

*Criteria fulfilled at least once per week for at least 2 months before diagnosis
Irritable Bowel Syndrome

• Symptoms that support the diagnosis
  – Abnormal stool frequency - >4/day or <2/week
  – Abnormal stool form
  – Abnormal stool passage – straining, urgency or incomplete evacuation
  – Passage of mucus
  – Bloating and abdominal distension

• Visceral hypersensitivity is documented in children with IBS (measure rectal tone)

• No controlled evidence supporting any therapy – Rome III, recent evidence...

Abdominal Migraine

1. Paroxysmal episodes of intense, acute periumbilical pain that lasts for 1 hour or more
2. Interfering periods of usual health lasting weeks to months
3. The pain interferes with normal activities
4. The pain is associated with 2 or more of the following:
   a. Aversion
   b. Nausea
   c. Vomiting
   d. Headache
   e. Photograph
5. No evidence of an inflammatory, systemic, constitutional, or anatomic process considered that explains the subject's symptoms

*Criteria fulfilled 2 or more times in the preceding 12 weeks

Abdominal Migraine

• Paroxysmal pain and absence of pain between episodes make chronic inflammatory disease unlikely

• Think about obstructive processes in urologic, digestive and biliary tract

• Avoid triggers

• Limited data suggest pizotifen (sandomigran – serotonin/histamine antagonist) may be effective prophylaxis
Childhood Functional Abdominal Pain

Must include all of the following:
1. Episodic or continuous abdominal pain
2. Insufficient criteria for other FGIDs
3. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject’s symptoms

*Criteria fulfilled at least once per week for at least 2 months before diagnosis

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Childhood Functional Abdominal Pain Syndrome

Must include childhood functional abdominal pain at least 25% of the time and 1 or more of the following:
1. Some loss of daily functioning
2. Additional somatic symptoms such as headache, limb pain, or difficulty sleeping

*Criteria fulfilled at least once per week for at least 2 months before diagnosis

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Functional Abdominal Pain

- Previous definitions required loss of function so did not capture motivated kids or parents who insisted on continued activity.
- Visceral hypersensitivity not documented in children (IBS has rectal hypersensitivity) but hypothesis is that may have proximal GI tract hypersensitivity
Functional Abdominal Pain:
Clinical Evaluation

- AAP Clinical report 2005 – children age 4-18 meeting the criteria, with normal exam and negative stool occult blood do not need additional tests.
- At the discretion of the clinician (depending on child’s most prominent symptoms and degree of parental anxiety)
  - CBC, ESR or CRP, urine
  - Liver enzymes
  - Lipase
  - Stool O & P, C &S

Functional Abdominal Pain
Treatment

- Biopsychosocial approach
- Reassurance and explanation of brain-gut interaction
- Role of psychosocial factors and triggers
- Medications
  - H2 blockers, or PPI
  - SSRI
  - amitriptyline

Biopsychosocial model

- Explain that FGID’s are true disorders related to abnormal sensations or disregulation of neuroenteric function and that it can be modified by psychological and pharmacological treatments
- Explain goals of treatment – improve function not necessarily cure – analogy of arthritis
- Keep symptom log including pain events, situation and emotional and cognitive response
Biopsychosocial model: Psychological treatment

- Cognitive/behavioural and stress management
- Explain that there are studies using functional MRI and PET scanning, that show this treatment decreases the activation from colon stimuli in the central emotional regions which are hyperactive in functional pain syndromes

Biopsychosocial model: Pharmacologic treatment

- SSRI’s and amitriptyline
- Patients need to understand that these drugs are central analgesics and increase the release of neurotransmitters that block pain transmission from the gut to the brain

GI Referral?

- Patients seen in tertiary care GI clinics vs community practice do not differ in pain scores, stooling patterns
- Maternal perception of child’s pain was higher in population seen by GI
- Costs, excluding endoscopy, were five times higher for GI vs community care
- No evidence of different outcomes
American Academy of Pediatrics: Subcommittee on chronic Abdominal Pain
Technical report and guidelines
March 2005
Attempt to answer several questions regarding Rome Criteria using an evidence based approach

eight questions

<table>
<thead>
<tr>
<th>Level</th>
<th>Criteria</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>Well-designed RCTs or diagnostic studies on relevant populations: 1-2 studies that compared the test with a criterion standard in an independent, blind manner in an unselected population of children similar to those addressed in the report</td>
</tr>
<tr>
<td>B</td>
<td>RCTs or diagnostic studies with minor limitations and overwhelmingly consistent evidence from observational studies: a single study that compared the test with a criterion standard in an independent, blind manner in an unselected population of children similar to those addressed in the report</td>
</tr>
<tr>
<td>C</td>
<td>Observational studies (case-control and cohort design)</td>
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<tr>
<td>D</td>
<td>Expert opinion, case reports, reasoning from first principles</td>
</tr>
</tbody>
</table>

Question 1: is there evidence that children with chronic abdominal pain have symptoms that can be categorized as functional dyspepsia, IBS or abdominal migraine

- Limited but credible evidence (quality C)
Question #2 – What is the predictive value of history items

- No studies showing that pain frequency, location, severity or effects on lifestyle distinguish functional from organic (LEVEL C)
- Children with recurrent abd pain have higher incidence of headache, joint pain, anorexia, nausea and altered bowel symptom (C)
- Alarm symptoms suggest higher incidence of organic disease and warrant investigation (D)

Question #3 – What is the predictive value of laboratory tests?

- No evidence to evaluate the predictive value of lab tests (D)
- No evidence to evaluate the predictive value of lab tests in the face of alarm symptoms (D)
- Lab markers for common GI problems eg. Lactose malabsorption or H pylori does not indicate a causal relationship and often does not cause the abdominal pain

Question #4 – What is the predictive value of other diagnostic tests?

- Ultrasound – no evidence has significant yield for organic disease (C)
  - Fewer that 1% of scans show an abnormality in patients with FGID’s using Rome III criteria
  - Schmidt 1993 – 57 US in pts with CAP, 56 were normal. One had ovarian cyst on opposite side of her pain which subsequently resolved but her pain did not
  - Yip 1998 – 5 abnormal scans of 598 children with typical RAP (0.8 %) of which 3 were not felt to be the cause of the pain (duplex ureter, low lying kidney) one was massive fecal impaction
Endoscopy and pH monitoring?

• No evidence of significant yield of organic disease (C)

Biomarkers?

• Lembo 2009 – panel of 10 serum biomarkers (cytokines, acute phase markers, immunoglobulin’s etc) 516 kids with IBS vs controls: ppv 81%, npv 64%, accuracy 70%
• Halac 2010 – barostat measurements of rectal sensitivity 94%, specificity 77%, accuracy 82%

Question #5 – What is the diagnostic value of a psychosocial history

• No difference in life stress, anxiety depression, or behavioral disorders in patients with FGID’s and controls with organic disease (ie can’t use to differentiate between organic and functional)
• Higher life stress, anxiety and depression in patients with FGID than healthy controls
Family functioning

- Mothers (but not fathers) of pts with FGID’s have significantly higher levels of anxiety, depression and somatization disorders
- Children with FGID’s have greater parental encouragement of illness behavior than children without abdominal pain

Question #6 – What is the effectiveness of pharmacologic treatment?

- Very few studies
- Dyspepsia – conflicting evidence but there may be benefit for H2-receptor antagonists and PPI
- IBS – inconclusive evidence for dietary changes
- Lactose intolerance – no difference in incidence in patients with FGID’s and controls, and no change in symptoms in lactose non-absorbers when go on elimination diets

Antidepressants

- Amitriptyline – Bahar 2008
  - Low dose RCT 33 patients with IBS – significant improvement in symptom scores and functioning
- SSRI – limited data support use in severe cases
Question #7 – What is the effectiveness of cognitive-behavioral therapy

- There is evidence that cognitive-behavioral therapy is useful in decreasing pain and improving function (B)
- Sanders 1994 – 44 patients assigned to cognitive therapy or standard pediatric care
  - Significantly more had complete elimination of pain and fewer relapses at 6 and 12 months
  - Children’s active self-coping and mothers’ caregiving strategies were significant independent predictors of pain behavior at post treatment.

Question #8 – What is the effectiveness of surgery

- No evidence of benefit

When presented with these cases in the Emergency we can answer families main worries:

- What is wrong with my child? – use positive criteria to Dx IBS, FAPS.
- Is it dangerous? – No
- Will it go away? – Will probably come and go
- What can we do? – Education and reassurance, +/- psychological Rx and medication