Pediatric Gastrointestinal Dysmotility Syndrome:

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CARTAGENA COLOMBIA
Boston Children’s Hospital

BCH first opened in 1869

BCH today with 395 beds

One of many BCH satellites bringing pediatric care to local communities
OUTLINE

1. PATHOPHYSIOLOGY
2. CLINICAL SYNDROMES
3. DIAGNOSIS
4. THERAPEUTIC INTERVENTIONS
5. SUMMARY
Pediatric GI Dysmotility Syndrome

• FOREGUT
  I. Esophageal Dysmotility
     (Achalasia, Esophageal spasm, Absent/weak peristalsis, Hypertensive peristalsis, EoE, GERD)
  II. Gastroparesis
  III. Gastric Accommodation Disorder
Pediatric GI Dysmotility Syndrome

• MIDGUT

I. Congenital and acquired Intestinal Pseudo Obstruction Syndrome (Neuro-Myopathic)
Pediatric GI Dysmotility Syndrome

• HINDGUT
  I. Hirschsprungs Disease and allied disorders
      (NID, Hypo/Hyper Ganglionosis)
  II. Intractable Constipation
  III. IAS Achalasia/ultra short segment Hirschprungs
Pathophysiology
Prevalence of Childhood Gastrointestinal Neuromuscular Disorders

- Chronic intestinal pseudo-obstruction
- Visceral pain disorder
- Munchausen’s syndrome-by-proxy
- Achalasia
- Hirschsprung’s disease
- Cyclic vomiting syndrome
- Toddler’s diarrhea
- Constipation
- Functional abdominal pain
- Infant regurgitation

Estimated cases per year:
- $10^3$
- $10^5$
- $10^6$
Dysmotility Symptoms

SENSORY

- Visceral Distention
- Perception

MOTILITY

- Esophageal
- Antro-Duodenal
- Ano Rectal
- Colonic

VISCERAL HYPERALGESIA

- Feeding Intolerance
- Abdominal Pain

QUALITY OF LIFE

Flores/Bell
GASTROINTESTINAL DYSMOTILITY

- EXTRINSEC PARA-SYMPATHETIC SYMPATHETIC
- NEURO ENDOCRINE CIRCUITRY
- INTERSTITIAL CELLS OF CAJAL
- INTRINSEC ENTERIC NERVOUS SYSTEM

SMOOTH MUSCLE
ALLERGY-INFLAMMATION AND GASTROINTESTINAL DYSMOTILITY

POTENTIAL MECHANISMS

1. Food Intolerance
   (Bioactive amines, exorphins)
2. Indirect Mechanism (gut flora)
3. Cell mediated responses (TH2 ABNL responses)
4. Mast cell/Macrophage Activation
   Mediator release: Histamine, 5-HT, cytokines, leukotrienes
5. Eosinophilic mediated responses
   (systemic IL-5 release and eotaxin expression)

Murch
J. Pediatric Gastroenterology Nutrition
Vol. 41: Supplement 1: 2005
INTERSTITIAL CELLS OF CAJAL (ICC’s)

- Mesenchymal cells present along the gastrointestinal tract characterized by receptor tyrosine kinase kit
- Source of the spontaneous slow waves of depolarization (pacemaker) recorded in the GI muscularis propria and also involved in neurotransmission
- Alteration of ICC distribution reported in several GI conditions: achalasia (LES/IAS), pyloric stenosis, Hirschsprung’s Disease, CIPO, colonic inertia

Kenny, Vanderwiden
Role of Intestinal Microbiota in Dysmotility

- Germ-free mice exhibit delayed gastric emptying, slower intestinal transit and more susceptible to enteric infections.
- Immune dysregulation (upregulation of Inflammatory markers such as T cells, cytokines, CRP and increase activated mast cells.)
- Post infectious IBS
- Response to probiotics in hyperalgesia.

Clinical Syndromes
CIPO - DEFINITION

Is a severe and disabling disorder characterized by episodes of continuous symptoms and signs of bowel obstruction in the absence of a fixed lumen occluding lesion.

Rudolph, Hyman, Flores
J. Pediatric Gastrointestinal Nutrition
1997: 24: 102 - 112
CIPO TIME LINE

- 1970: Maldonado. CIPO Term. Am J. Medicine
- 1981: Schuffler. CIPO syndrome (Histology) Med Clin NA.
- 1999: Grant/Kocoshis. Intestinal Tx in CIPO Transplantation. GUT
- 2000’s: Prokinetics/Nutrition support (ACE, Botox, Jejunostomy)
EPIDEMIOLOGY (I)

- Presentation during 1\textsuperscript{st} year of life (43 % in 1\textsuperscript{st} month)
- Transient form in prematures
- 25\% mortality rate at a median follow-up time of 2 years
- Midgut malrotation, short bowel, urinary tract involvement, onset under 1 year of age and myopathy are poor prognostic factors.

Vargas & Ament
J. Pediatric Gastrointestinal Nutrition
1988; 7: 323 - 332
EPIDEMIOLOGY (II)

- Family history is significant in up to 29%.
- Hypogammaglobulinemia and immunodeficiencies are present in up to 78% of patients with CIPO.
- Biliary tract motility abnormalities and sphincter of Oddi dysfunction are present in patients with CIPO.
- Association with Autoimmune Hepatitis and Leiomyositis has been reported.

Mousa, Hyman, Flores
Diagnostic Disease Science
2002: 47: 2298-2305
• Actin: gamma - enteric smooth muscle protein encoded by the ACTG2 Gene.
• Involve in cell motility and contractility as well as cytoskeleton maintenance.
• Specific for CIPO, visceral myopathy and micro colon-megacystis – Hypoperistalsis (Berdon Syndrome)
• Gene testing available: a.milunsky@CHginc.org
• Mitochondrial genome sequencing and deletion testing is also available (MELAS, MNGIE, MERRF)
ETIOLOGY
1. PRIMARY DISORDERS

A. Familial Visceral Myopathy
   - Type I (recessive) (Megacystis syndrome)
   - Type II (dominant) (Mitochondropathies)
   - Type III (Fatal)

B. Familial Visceral Neuropathy
   - Type I (recessive) (Gastroparesis)
   - Type II (dominant) (Short bowel, Malrotation)
2. Secondary Disorders

A. Collagen Vascular
   (Lupus, Dermatomyositis)
B. Neuromuscular
   (Amyloid, Diabetic Neuropathy, Neurofibromatosis,
   MS, IND, Ganglionitis, Leiomyositis)
C. Infectious
   (Chagas, CMV, EBV, Rotavirus, Norovirus, Herpes)
D. Miscellaneous
   (Fetal ETOH syndrome, extensive Crohn’s, ICC (Cajal)
    deficiency, post radiation/chemotherapy, EGE, post BM/stem cell
    tx, autoimmune gastrointestinal dysmotility (AGID)
CIPO VARIABLES

1. Age of onset (congenital or acquired)
2. Clinical Presentation (vomiting, distension, constipation)
3. Course of Disease (constant, intermittent, cyclic)
4. Systems involved (mono or polystemic)
5. GI tract Involvement (segmental, pan gastrointestinal)
6. Pathology findings (neuropathy vs. myopathy)
Clinical Syndromes II

1. Post surgical Hirschsprung’s Disease
2. Post viral gastro duodenoparesis
3. Cyclic vomiting/migraine disease
4. Intestinal pseudo obstruction syndrome (neuro and myopathic)
4. Autonomic nervous system dysfunction syndrome
Chronic intestinal pseudo-obstruction is a clinical diagnosis, based on signs and symptoms.
Manifestations

- Abd. distention after meals
- Nausea and vomiting
- Alternating diarrhea and constipation
- Abdominal pain
- Failure to thrive
- Swallowing difficulties
- Urinary problems
CIPO

Extraintestinal Manifestations

1. Urinary bladder: 44%
2. Developmental Delay: 40%
3. Dysautonomia: 22%
4. Food Allergies: 17%
CIPO

**Sites of Involvement**

1. Esophagus: 32%
2. Stomach: 76%
3. Small Bowel: 87%
4. Colon: 60%
# Chronic Intestinal Pseudo-Obstruction

## Children:
- Mostly primary
- Mostly congenital
- Neuropathy more common than Myopathy
- Neuropathy secondary to maturational arrest of the myenteric plexus
- TPN frequently needed
- Absence of MMC predicts need for TPN
- Presence of MMC predicts response to prokinetics
- Death likely due to complications of TPN

## Adults:
- Mostly secondary
- Mostly acquired
- Myopathy more common than Neuropathy
- TPN rarely needed
- Absence of MMC not predictive
- Normal autonomic function predicts response to prokinetics
- Death likely due to primary disease
ABDOMINAL PAIN

Functional Abdominal Pain

- Pain constant or nearly constant
- At least 6 months
- Not associated with systemic disease
- If associated with eating or BM, consider functional dyspepsia or IBS
- Usually no alarm symptoms
- Normal GI studies

Chronic Intestinal Pseudo-obstruction

- Pain is not a constant feature
- May have episodes that mimic acute obstruction
- Often associated with systemic disease
- May have diarrhea and weight loss secondary to bacterial overgrowth
- Abnormal GI studies
CIPO – LONG TERM OUTCOME

POPULATION
- 85 children over 10 years
- 14% premature
- 41% GU involvement (myopathy)
- 32 patients Myopathic
- 48 patients Neuropathic
- 5 patients mixed
- 10 patients with malrotation

NUTRITION SUPPORT
- 62% TPN dependent
- 38% TPN + enteral

SURVIVAL
- 25 month period
- 25 died (TPN related complications)
- 5 died after small bowel transplant

Mousa, Hyman, Flores
Digestive Diseases and Sciences
47: 2298-2305, 2002
Diagnosis
Radiological Evaluation

1. Upper G.I. and small bowel follow through
2. Barium enema

Nuclear Medicine

1. Radioisotopic gastric emptying (solid and liquid)
MELAS
1. Duodenal (light microscopy and disaccharidases)
2. Rectal (amyloid, presence of ganglion cells, neuronal dysplasia)
3. Full thickness intestinal biopsies
Motility Studies

Esophageal
Ano-Rectal
Antro-Duodenal
Colonic
Electrogastrography
Abnormalities of Gastrointestinal Contractility

1. Weak or absent contractions
2. Loss of peristaltic control and impaired transport
3. Failure of sphincters
4. Occurrence of spontaneous uncoordinated contractions
5. Loss of migrating motor complex
Interdigestive Migrating Motor Complex (MMC)

A.K.A. Intestinal Housekeeper

Cyclic group of phasic contractions of the small intestine organized as a recurrent pattern of different phases.

Szurszowski, jh: am.j physiol 217:1757-1763.1969
Antral Motility Sequence
ANTRODUODENAL MANOMETRY 6-14

INDICATIONS

1. To assess antroduodenal motility in children with chronic intestinal pseudo-obstruction and gastroparesis.

2. To assess antroduodenal motility when colectomy is considered for intractable constipation.

3. To distinguish between rumination and vomiting.

4. To assess antroduodenal motility in children with unexplained symptoms that might be related to motility problems.

DiLorenzo
Perfusion Catheter
Auto Duodenal Manometry

Endoscopic or fluoroscopic placement

Provocative testing (Drugs)

Meal

Fasting recording 2-4 hours

Drug effect 1 hour

Post prandial recording 2-3 hours
ABSENT POST PRANDIAL MOTOR ACTIVITY

antrum

proximal duodenum

mid duodenum

5 min

50 mmHg
RETROGRADE PHASE 3-LIKE ACTIVITY

antrum

mid duodenum

3 minutes

50mm Hg

distal duodenum
ADM
Normal EES response
Antro Duodenal Manometry (I)
Manometric features of Antro Duodenal Motility Disorders

<table>
<thead>
<tr>
<th>Motility disorders</th>
<th>Main characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal myopathy ................................</td>
<td>Persistently low-amplitude (&lt;20 mmHg)</td>
</tr>
<tr>
<td>Intestinal neuropathy ............................</td>
<td>Coordinated contractions in the absence of dilated bowel</td>
</tr>
<tr>
<td>Rumination ........................................</td>
<td>Normal amplitude but abnormal patterns of contractions</td>
</tr>
<tr>
<td>Postprandial hypomotility ........................</td>
<td>Pattern of brief, simultaneous pressure</td>
</tr>
<tr>
<td></td>
<td>Increase in all recording sites associated</td>
</tr>
<tr>
<td></td>
<td>With regurgitation R waves</td>
</tr>
<tr>
<td></td>
<td>Motility index &lt;600 mmHg/30min after Ingestion of meal</td>
</tr>
</tbody>
</table>
Antro Duodenal Manometry (I)
Manometric features of Antro Duodenal Motility Disorders

Motility disorders

- Failure to induce fed pattern
- Mechanical intestinal obstruction

Main characteristics

- Occurrence of phase III of the MMC with
  In 2 h after ingestion of meal
- Prolonged simultaneous non-propagating
  Contractions
- Postprandial clustered contractions
  lasting > 30 minutes
- Neonates: High amplitude retrograde
  propagating contractions
Antro Duodenal Manometry (II)

- 35 ADM recordings from children 0.3 to 18 years evaluated independently by 5 Pedi GI MD’s
- Cohens KAPPA calculated
- Observers were unanimous on the differentiation of NL and ABNL
- Excellent inter-observer agreement regarding Phase III episodes (KAPPA = 0.82)

Kappa: > 0.4 = good agreement
> 0.75 = excellent agreement

Connor et al
Neurogastroenterol Matic
(2009, 21, 500-503)
Comparison of Inter-observer variability

1. Antro Duodenal Motility: $K : 0.57$
2. IBD/Histology : $K : 0.47$
3. NEC (imaging) : $K : 0.31$
4. Reflux esophagitis (Endoscopy) : $K : 0.56$
17 patients were investigated for 2 consecutive days

Parameters: (1.) Motility index (2.) Phase duration (3.) Presence of Phase III (MMC) (4.) Response to EES and Octreotide

Dx: CIPO (88%), SBS (12%)
RESULTS

• No parameter changed from normal on day 1 to abnormal on day 2.
• Of 13 patients with an abnormal ADM on day 1, 6 of them were normal on day 2.
• Overall change of interpretation from abnormal to normal (35%)

CONCLUSION

• There was a significant increase in MI from antrum and SB from day 1 to day 2 suggesting anesthesia effect.
Diagnosis
Electrogastrography

- Noninvasive test to measure the gastric myoelectrical activity

- Abnormal variation of 3 CPM, dominant power and post-prandial bradygastria

- Gastric dysrhythmias in 72-93%
Fig. 1: Functional components of the stomach in gastric emptying.
Gastric Pacemaker (4 cpm)
SMART PILL

• Requires **NO** specialist technical skills
• Office based test
• Ability to monitor multiple parameters simultaneously (pH, pressure & temperature)
• Determines: Gastric emptying time
• total transit for stomach, small bowel and colon,
• motility indices
• High degree of correlation to gastric emptying scintigraphy

KUO
Gastroenterology
2006; (suppl Z) 434
SmartPill Tracing

THERAPY
THERAPEUTIC INTERVENTIONS

• MEDICAL I: PROKINETICS

1. Dopamine receptor antagonists
   - metoclopramide (D₂ antagonist & 5HT4 agonist)
   - domperidone (similar action/no penetration to blood – brain barrier)

2. Motilin Receptor Agonists
   - Erythromycin,
   - Azithromycin,
   - Clarithromycin
3. 5 Hydroxytryptamine type 4 receptor agonists
   - cisapride
   - tegaserod
   - prucalopride
   - velusetrag
4. Cholinesterase Inhibitors
   - Neostigmine
   - pyridostigmine
16 children with CIPO, TPN dependent.

Response: Enteral feeding increase of $\geq 10$cc/kg/day

RESULTS:

- Feed increase in 69% (11/16)
- Responders 44% (7/16)
  - $\rightarrow$ 3 – off TPN
  - $\rightarrow$ 1 – $> 30$cc/kg/day
  - $\rightarrow$ 3 – tolerated 10-12cc/kg/day
- Association between response and presence of MMC and increase Motility Index

CONCLUSION: Octreotide is effective in improving enteral tolerance.
NEW EMERGING PRO-KINETICS

• PAMORA: (Peripherally acting Mu-opioid receptor antagonistic)
  - Increase colonic transit and motility
  - *naloxegol* (MOVANTIK™)

• GHRELIN AGONISTS
  - Promote gastric and colonic motility
  - Gastric accommodation increased
  - *relamorelin* (synthetic Penta Peptide)

Camilleri
Neurogast Motil
(2014) 26, 1070-1078
THERAPEUTIC INTERVENTIONS I

- MEDICAL II: ANTIBIOTICS
  1. Amoxicillin/clavulonic acid (MMC induction)
  2. Metronidazole (SBO)
  3. Rifaximin (SBO, IBS-D)
  4. anti-fungals
cyproheptadine (serotonin antagonist)
  via regulation of receptive relaxation
**THERAPEUTIC INTERVENTIONS II**

<table>
<thead>
<tr>
<th>C. Unconventional</th>
<th>E. Psycho-Social Family Support</th>
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<tbody>
<tr>
<td>• Intrasphincteric Botox injection (pylorus/IAS)</td>
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<tr>
<td>• Gastric pacing</td>
<td>F. Pain control and Stress Management</td>
</tr>
<tr>
<td>D. Nutrition Support</td>
<td>• Behavioral/Relaxation Therapy</td>
</tr>
<tr>
<td>• Gastrostomy</td>
<td>• Tricyclic Antidepressants</td>
</tr>
<tr>
<td>• Jejunostomy</td>
<td>• Cannabinoids</td>
</tr>
<tr>
<td>• Total Parenteral Nutrition (MediPort/Broviac)</td>
<td>• Acupuncture</td>
</tr>
</tbody>
</table>
Jejunal Intussusception
NAUSEA CONTROL

• Use of IV or PO Ondansetron and Granisetron
• Domperidone and Metoclopramide have superior action
• Ondasetron suppositories
• Prochlorperazine/Phenergan have limited role due to side effects
• Scopalamine Patch
ACID CONTROL

• Important to treat given high frequency of GER/Gastritis
• Combination $H_2$ blockers with TPN
• Combination $H_2$ blockers and PPI’s
• Sulcrafate for alkaline reflux
SURGICAL THERAPY CIPO

- Segmental resections and bypass procedures are discouraged
- Gastrostomy for venting
- Distal jejunostomy for feeding
- Enterectomy /TPN
- Intestinal transplantation
- Gastric pacing
Nutrition Support

- Ultimate aim is to ascertain that the patient reaches a normal growth and development
- Avoid serious nutrient deficiencies and protein calorie malnutrition
- CIPO patients: 1/3 require TPN or PTPN
  - 1/3 require partial enteral support (G/J tube)
  - 30 % Neuropathy need TPN
  - 70 % Myopathy need TPN
- Vital to use enteral route (Liver protection, pancreatic activity, Immune response, trophic factors)
- Use of continuous feedings via Gastrostomy and Jejunostomy

DiLorenzo, Flores, Hyman
FORMULAS

1. Alimentum®, Nutramigen® (casein based)
2. Pediasure® Peptide (whey protein, MCT/LCT, structured lipids, Nutraflora® FOS® prebiotic, sucrose, corn starch)
3. Peptamen® (whey protein)
4. Vivonex® (elemental)
5. Osmolite®
6. EleCare® (amino acid)
INTESTINAL TRANSPLANTATION

- Indicated in TPN dependent CIPO patients with TPN complications (recurrent sepsis, fungemia, thromboembolic events, cholestatic liver disease and cirrhosis)
- Outcomes in patients with CIPO have improved with new immuno suppression (sirolium)
- 83% one year survival in children < 2 years
- 90% one year survival in children > 2 years
- Urological and long standing visceral hyperalgesia complicates post operative recovery

Sigurasson & Di Lorenzo
Gut: 1999; 45: 570, 574
Intestinal Transplantation

- Indications:
  - 63% Short gut
  - 18% Motility Disorders
  - 8% Malabsorption
  - 1% Tumors
  - 8% Re-Transplant
- 100% 1 year survival
- 95% 5 year survival

- Improvements Due To:
  - Better surgical techniques
  - Better Patient selection
  - Better Immunosuppression
  - Better anti-viral strategies

Kocoshis
Cincinnati Children’s Hospital
SUMMARY

• CIPO may be seen as the end spectrum of GI dysmotility disorders and still carries significant morbidity and mortality
• Always rule out mechanical obstruction, pediatric falsification, Munchausen by proxy and disabling pain disorder before invasive treatments are implemented
• Tissue diagnosis only when a surgical procedure is indicated
• Enteral feeding preferred over TPN
• Palliative surgical procedures only when clinically indicated
• Intestinal transplantation may develop into the optimal therapy for irreversible intestinal failure
1. PEDS (Pediatric Digestion and Motility Disorder Society, Inc.) info at pedsgi.org
2. AGMD (Association of Gastrointestinal Motility Disorders, Inc.)
   www.agmd-gimotility.org
3. International Foundation for Functional Gastrointestinal Disorders
   www.iffgd.org
THE END