Intestinal Pseudo-obstruction (Gut Motility Disorders)

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Gastrointestinal Tract
functions dependent on gut motility
Gut Motility
complex regional patterns

Gut Motility Disorders
failure of gut neuromusculature
Paediatric Gastrointestinal Motility Disorders
rare, diverse and challenging

1:500,000

Oesophageal Achalasia

1:100,000

Intestinal Pseudo-obstruction

1:5,000

Hirschsprung's disease

Intractable or slow transit constipation

Anal Incontinence

Burns & Thapar (2014)
Nature Reviews Gastro Hepatol
Chronic Intestinal Pseudo-obstruction
Failure of function of the small intestine

- Symptoms/signs of small intestinal obstruction but no mechanical cause
- Dilated small intestine with fluid levels
In infants CIPO appears to have a particularly severe course
- 60%–80% requiring parenteral nutrition and
   Faure et al. Dig Dis Sci 1999
   Muto et al. JPS 2014

**Intestinal transplantation**

Soh et al. JPS 2015
Paediatric Intestinal Pseudo-obstruction
Great Ormond Street Hospital data pre-2012

Delayed referral and/or diagnosis
• 11.3 years

Repeated unnecessary abdominal surgeries
• 3-5 surgeries before referral to tertiary centre

Poor feed tolerance
• ~100% on parenteral nutrition

Complications (morbidity, hospitalisation days, mortality)
• 90 days a year in hospital, 20-30% mortality, PN related complications

Poor quality of life
Paediatric Intestinal Pseudo-obstruction
Epidemiology

North America - NASPGHAN Survey
- 100 infants are born in the United States every year with CIPO
- incidence of approximately 1 per 40,000 live births
- Equal sex incidence

Japan - Nationwide survey
- children younger than 15 years of age the prevalence of 3.7 in one million children (1 in 270,000 children)
- 56.5% developed CIPO in the neonatal period
- Equal sex incidence

Vargas et al JPGN 1988
Muto et al. JPS 2014
Paediatric Intestinal Pseudo-obstruction

Pharmacotherapy

- Anticholinesterase inhibitors
  - Neostigmine, Pyridostigmine, Donepezil
- 5HT$_4$ Receptor Agonists
  - (Cisapride, Tegaserod withdrawn)
  - Prucalopride
  - TD-5108
- Motilin Agonists / Ghrelins
- Octreotide
- Cannabinoids
- Opioid Receptor Antagonists
- Chloride Channel Activators
  - Lubiprostone
- Guanylate Cyclase Receptor Agonists
  - Linaclotide
- Antibiotics
Paediatric Intestinal Pseudo-obstruction

Pharmacotherapy

- Anticholinesterase inhibitors
  - Neostigmine, Pyridostigmine, Donepezil
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  - Lubiprostone
- Guanylate Cyclase Receptor Agonists
  - Linaclotide
- Antibiotics

Not tested in Children
Variable Efficacy
Unacceptable extra-intestinal Side Effects
Paediatric Intestinal Pseudo-obstruction Management

• Nutrition to preserve growth and development
  – Enteral feeds
  – PN

• Limit symptoms & improve quality of life
  – Medical Rx
  – Surgery
  – Psychology

• Prevent complications
  – Sepsis
  – Bacterial Overgrowth
Chronic Intestinal Pseudo-obstruction
Challenges

- Rare
  - need for national/international registries
  - collaboration

- Lack of clarity
  - aetiopathogenesis
  - diagnostic criteria
  - classification

- Lack of uniformity
  - available expertise
  - diagnostic protocols
  - management strategies
### Table 1: Role of molecules produced by the gut mesenchyme or epithelium in ENS development

<table>
<thead>
<tr>
<th>Secreted ligand</th>
<th>Role in ENCCs</th>
<th>Phenotype of mouse ENS after perturbation</th>
<th>Evidence for role in Hirschsprung disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDNF (mesenchymal)</td>
<td>Promotes differentiation</td>
<td>Yes&lt;sup&gt;498&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Endothelin-3 (mesenchymal)</td>
<td>Promotes proliferation and migration; Edn3&lt;sup&gt;-/-&lt;/sup&gt;: normal enteric neuron density&lt;sup&gt;105&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;90,152&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Role of cell-surface molecules expressed by ENCCs in ENS development

<table>
<thead>
<tr>
<th>Cell-surface molecule</th>
<th>Role in ENCCs</th>
<th>Phenotype of mouse ENS after perturbation</th>
<th>Evidence for role in Hirschsprung disease</th>
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</thead>
<tbody>
<tr>
<td>RET</td>
<td>Signaling</td>
<td>Tachyphylaxis&lt;sup&gt;165&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;49&lt;/sup&gt;</td>
</tr>
<tr>
<td>GFRA1</td>
<td>GPI linked GDNF receptor&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Gfra1&lt;sup&gt;−/−&lt;/sup&gt;: normal ENS&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;347&lt;/sup&gt;</td>
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<tr>
<td>GFRA2</td>
<td></td>
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<tr>
<td>ECE1</td>
<td></td>
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<tr>
<td>Neurotrophin-3 (mesenchymal)</td>
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<tr>
<td>Sonic hedgehog (mesenchymal)</td>
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<tr>
<td>Indian hedgehog (epithelial)</td>
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<tr>
<td>BMP2 and BMP4 (mesenchymal)</td>
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<tr>
<td>Netrin (epithelial)</td>
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<tr>
<td>Semaphorin 3C (mesenchymal)</td>
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<tr>
<td>Neurturin (mesenchymal)</td>
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<tr>
<td>GGF2</td>
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<td>Yes&lt;sup&gt;347&lt;/sup&gt;</td>
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</table>

### Table 3: Transcription factors and cofactors expressed by ENCCs and their role in ENS development

<table>
<thead>
<tr>
<th>Transcription factor</th>
<th>Role in ENCCs</th>
<th>Phenotype of mouse ENS after perturbation</th>
<th>Evidence for role in Hirschsprung disease</th>
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</thead>
<tbody>
<tr>
<td>Sox10</td>
<td>Progenitor</td>
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<tr>
<td>TrkB</td>
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<tr>
<td>Sox8</td>
<td>Acts with Sox10, maintains progenitors&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Sox&lt;sup&gt;8&lt;/sup&gt; or Sox&lt;sup&gt;8&lt;/sup&gt;−/−: Increases severity and penetrance of Sox&lt;sup&gt;8&lt;/sup&gt;−/− phenotype&lt;sup&gt;55&lt;/sup&gt;</td>
<td>ND</td>
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<tr>
<td>GFRα1</td>
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<tr>
<td>Notch</td>
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<tr>
<td>PTCH1</td>
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<tr>
<td>β1-integrin (ITB1)</td>
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<tr>
<td>L1-CAM</td>
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<td>SAP1</td>
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<tr>
<td>N-cadherin</td>
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<tr>
<td>Neuregulin-1</td>
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<td>Hoxb5</td>
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### Table 4: ENCC intracellular molecules, neurotransmitter-related molecules and dietary factors involved in ENS development

<table>
<thead>
<tr>
<th>Intracellular molecule</th>
<th>Role in ENCCs</th>
<th>Phenotype of mouse ENS after perturbation</th>
<th>Evidence for role in Hirschsprung disease</th>
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<tbody>
<tr>
<td>Intracellular molecule</td>
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<tr>
<td>SPRY2</td>
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<tr>
<td>Asd1&lt;sup&gt;1&lt;/sup&gt; (Mash1)</td>
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<tr>
<td>PTEN</td>
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<tr>
<td>N-cadherin</td>
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<tr>
<td>Neuregulin-1</td>
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<tr>
<td>Hoxb5</td>
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<tr>
<td>Intracellular molecule</td>
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</table>

### Cell Signalling Pathways

- **Gut Environmental Factors**
- **Transcription Factors**
- **Intracellular Molecules**
Neuro-immune interactions
role in gastrointestinal symptoms/disease

Ye et al
2008 J Cell Mol Med

Smyth et al
2013 Plos One

Serotonin (5H13, 5H1P)
PAR 1, 2 and 4
Histamine 1-4
CAM 1
IL-4
IL-13
Eotaxin
Eotaxin
IL-3
IL-5
GM-CSF
Etc...
Etc...
Etc...
Leukotrienes
MBP
Etc...

CGRP
Substance P
Acetylcholine
Noradrenaline

IL-4, 5, 13, TNF
Neuro-immune-microbiome interactions
role in gastrointestinal symptoms/disease

Ye et al
2008 J Cell Mol Med

Smyth et al
2013 Plos One

The Gut Microbiota

Serotonin (5HT₃, 5HT₁P)
PAR 1, 2 and 4
Histamine 1-4
CAM 1
IL-4
IL-13
Eotaxin
IL-3
IL-5
GM-CSF
Etc…

Leukotrienes
MBP
Etc…

IL-9
IL-4
IL-13
Etc…

Eotaxin
IL-9
IL-4, 13
Etc…

IL-4, 13
Etc…

GM-5

IL-4, 5, 13, TNF
Neuro-immune-microbiome-brain interactions role in gastrointestinal symptoms/disease

Serotonin (5HT3, 5HT1P)
PAR 1, 2 and 4
Histamine 1-4
CAM 1
IL-4
IL-13
Etc...

IL-9
IL-4
IL-13
Etc...

Eotaxin
Substance P
Acetylcholine

Gut Microbiota

Ye et al
2008 J Cell Mol Med

Smyth et al
2013 Plos One

Leukotrienes
MBP
Etc...

Eotaxin
IL-3
IL-5
GM-CSF

IL-4, 5, 13, T cells
Human studies

In vivo transplantation of post-natal neural stem cells

Dissociation into single cells

Rag2⁻/γc⁻/C5⁻ mouse

Natarajan et al, Neurogastroenterol Motil 2014