Hirschsprung’s Disease
A congenital condition characterized by the absence of ganglion cells in the submucosal (Meissner’s) and myenteric (Auerbach’s) plexus of the distal small bowel

- The length of intestine involved varies

- Functional obstruction results
History

- 1691: First description of megacolon in children by Ruysch, a Dutch anatomist
- 1886: Pathologic features described by Harold Hirschsprung at Berlin Society of Pediatrics
  - “Constipation in Newborns Due to Dilatation and Hypertrophy of the Colon”
- 1901: Tittel identified absence of ganglion cells in the distal colon of a child with Hirschsprung’s disease
  - First insight into pathogenesis
History

- 1938: Robertson and Kernohan defined the association of distal aganglionos and intestinal obstruction
- 1946: Ehrenpreis first to appreciate that colon became secondarily dilated owing to distal obstruction
- 1948: Swenson and Bill reported the first definitive operation for this condition
  - First to advocate full-thickness rectal biopsy for definitive diagnosis
Declining mortality rates:

- **1954:** Klein and Scarborough reported a 70% mortality rate
  - Mean age at diagnosis 45 months
- **1966:** Shimm and Swenson reported a 33% mortality rate
  - Mean age at diagnosis 6 months
- **1992:** Rescorla reported a 6% mortality rate
- **2000:** Teitelbaum reported a 1% mortality rate
Statistics

- Incidence approximately 1 in 5000 live births
- Male to female ratio 4:1
- Disease restricted to the rectosigmoid junction in 75%
- 20% have associated abnormalities: Down syndrome (8%), cardiac defects (8%), genitourinary abnormalities (6%), gastrointestinal abnormalities (4%)
Total colonic aganglionosis
Short segment aganglionosis
Neuronal intestinal dysplasia
Pathogenesis

- Inherited disorder with incomplete penetrance and variable expressivity
- Believed to be a defect of craniocaudal migration of neuroblasts originating from the neural crest
  - Normally complete by 12th week of gestation
- The earlier the migration arrest, the longer the aganglionic segment

Pathogenesis

Other hypotheses include defects of neuroblast differentiation into ganglion cells and accelerated ganglion cell destruction within the intestines
Pathogenesis: Genetics

- *RET* proto-oncogene strongly associated with Hirschsprung’s by family studies
  - Located on long arm of chromosome 10
  - Encodes a receptor tyrosine kinase
  - Mutated in 20% of Hirschsprung’s cases
  - Also mutated in MEN-2; higher incidents of Hirschsprung’s in these patients

Pathogenesis: Genetics

- Glial cell line-derived neurotrophic factor (GDNF) is a RET receptor ligand
  - Mutations in the GDNF gene may account for additional Hirschsprung’s cases

- Other genes identified:
  - Endothelin 3
  - Endothelin B receptor
  - Endothelin converting enzyme 1
  - SOX10 transcription factor

**Pathogenesis: Genetics**

- Known genetic mutations associated with Hirschsprung’s Disease:

<table>
<thead>
<tr>
<th>Predominant Name</th>
<th>Model or Human</th>
<th>Chromosome</th>
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<tbody>
<tr>
<td>Endothelin receptor B gene</td>
<td>Mouse and rat, Humans</td>
<td>13q22</td>
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<tr>
<td>Endothelin-3 gene</td>
<td>Mouse and rat, 2 human cases</td>
<td>20q13.2-q13.3</td>
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<td>SOX10/sox10 gene</td>
<td>Mouse, Human</td>
<td>22q12-q13</td>
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<td>Ret proto-oncogene</td>
<td>Mouse, Humans</td>
<td>10q11.2</td>
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<td>GDNF gene</td>
<td>Mouse, Humans</td>
<td>5p12-p13.1</td>
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<tr>
<td>Neuturin</td>
<td>Mouse, Humans</td>
<td>2q22-q23</td>
</tr>
<tr>
<td>Not identified LICAM gene</td>
<td>Human, Humans</td>
<td>20p11.22-p11.23 Exon 18 of LICAM gene</td>
</tr>
</tbody>
</table>
Diagnosis

Should be suspected in:

- any infant who doesn’t pass meconium within the first 24 hours of life
- newborn intestinal obstruction
- constipation / chronic abdominal distention in the first year of life
Diagnosis

Differential diagnosis:

- Includes all causes of mechanical and functional bowel obstruction in the neonate:
  - Mechanical obstruction:
    - Meconium ileus
    - Meconium plug syndrome
    - Neonatal small left colon syndrome
    - Malrotation with volvulus
    - Incarcerated hernia
    - Jejunoileal atresia
    - Colonic atresia
    - Intestinal duplication
    - Intussusception
    - NEC
Differential diagnosis:

- Includes all causes of mechanical and functional bowel obstruction in the neonate:
  - Functional obstruction:
    - Sepsis
    - Intracranial hemorrhage
    - Hypothyroidism
    - Maternal drug ingestion or addiction
    - Adrenal hemorrhage
    - Hypermagnesemia
    - Hypokalemia
Diagnosis

- Workup:
  - Physical exam, including rectal exam
  - Abdominal plain films
Diagnosis

- **Workup:**
  - Barium enema
    - In normal patients the caliber of the rectum should be equal to or greater than the rest of the colon
    - Hallmark finding is conical transition from distal nondilated colon or rectum to proximal dilated colon
Diagnosis

Workup (continued)

- Anorectal manometry
  - High pressure peristalsis in proximal ganglionic bowel
  - Lack of progressive peristalsis in a normal pressure zone lacking ganglion cells
  - Failure of relaxation of rectal sphincter in response to rectal distention
  - Rarely used as primary diagnostic modality. Valuable for evaluating functional results after reconstructive procedures
Diagnosis

- Workup (continued)
  - Biopsy
    - Full thickness biopsy gold standard. However, requires general anesthesia
    - Suction biopsy popular. Requires skilled pathologists and adequate specimen
    - Biopsy samples should be 2 to 3 cm above dentate line
Management

- Depends on prompt diagnosis and early treatment

- Initial management:
  - Prompt decompression with large-bore rectal tube with side holes
  - *Serial* washouts several times a day
  - Broad spectrum antibiotics, IV fluids
Enterocolitis

- Most feared complication of Hirschsprung’s disease
- Responsible for much of the associated mortality
- Etiology not yet elucidated
  - Several infectious agents and mucosal defensive elements have been investigated
Enterocolitis

Clinical signs and symptoms:

- Early: Abdominal distention, borborygmus, diarrhea
- May progress to fever, emesis, explosive diarrhea, fluid/electrolyte disorders, gram-negative sepsis, colonic perforation
Management

Dictated by presence or absence of enterocolitis

- Enterocolitis mandates emergent diverting colostomy
- Historically right transverse colostomy performed in all
  - Advantages: Faster (no intraop frozen sections required), protects subsequent pullthrough
  - Disadvantage: Three trips to OR needed
- Transition-zone colostomy now favored
One-stage procedure has gained favor

- First successful report by So et al in 1980
- Preparation:
  - Serial saline rectal washouts
  - Digital rectal dilatations
  - Last preop rectal washout with 1% neomycin
  - IV antibiotics for entire perioperative period

Management

- One-stage procedure:
  - Safe, cost-effective, avoids ostomy complications\(^1\)
    - However, relatively few data available regarding long-term outcome (particularly stooling patterns)
  - Level of aganglionosis established with frozen section
    - Role of pathologist pivotal to success of one stage approach

Management

- One-stage procedure:
  - Accepted contraindications include:
    - Enterocolitis with poor clinical patient status
    - Delayed diagnosis with resulting proximal dilatation
  - Down’s Syndrome
    - Often cited as contraindication due to early reports of increased complication and mortality rates
    - This has been disputed\(^1\)

Definitive Procedures

- Success depends on the ability to place bowel that contains ganglion cells within 1 cm of the anal verge.
- All currently utilized procedures have produced good results. All have produced complications.
- Surgeon experience and bias affect results.
Definitive Procedures
Definitive Procedures
Definitive Procedures
Conclusion

- Hirschsprung’s disease is a defined clinical entity with an unclear etiology.
- Successful management depends on early diagnosis, surgical expertise, and multidisciplinary support.
- Current trends are toward one-stage management but definitive supportive evidence is lacking.