Hirschsprung's Disease

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Harold Hirschsprung (1830–1916) presented his description of a disease later to bear his name to a pediatric congress in Berlin in 1886. He described two children, who died at 8 and 11 months of age, related to repeated attacks of enterocolitis.

23.1 Epidemiology

- 1 in 5000 live births.
- >90% of cases are diagnosed in the neonatal period.
- Approximately 5% of patients with HD are diagnosed after the first year of life.
- Two distinct clinical types with genetic differences (*vide infra).*
- *Short segment* (i.e., recto-sigmoid) 80% (M:F 3:1).
- *Long segment* 20% (M = F).

  Associated anomalies variable incidence ~10%

- Down's syndrome (~5%).

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- Neurocristopathies.
  - Waardenburg–Shah syndrome—white forelock, bicolored iris, deafness.
  - Hypoventilation syndrome (Ondine's curse[1])—association with HD termed Haddad syndrome.
- Mental retardation syndromes.
  - Smith-Lemli-Opitz syndrome—mental retardation, polydactyl, defect in cholesterol metabolism.
  - Mowat-Wilson syndrome—mental retardation, characteristic facies.
- Development colon anomalies.
  - Colon atresia, anorectal atresia.
- Miscellaneous.
  - Kaufman-McKusick syndrome—hydrometrocolpos, hypospadias, polydactyl.

N.B**. Multiple Endocrine Neoplasia (MEN) type 2B** (Marfanoid habitus, medullary thyroid cancer, café au lait spots, mucosal neuroma) is associated with ***hyperganglionosis*** (but functionally similar to HD).

23.2 Embryology

Migration of neurenteric cells from the neural crest to GI tract—aborally.

1. Esophagus fifth-week gestation.
2. Mid-gut seventh-week gestation.
3. Distal colon by 12th-week gestation.

Some studies suggest that ganglion cells are guided to their destination by neural glycoproteins or fibers (e.g., fibronectin and hyaluronic acid).

23.3 Anatomy and Neuroanatomy

The normal intestinal wall contains two distinct nerve plexi, between three muscle layers (longitudinal, circular, muscularis mucosae). These are:

- Submucosal plexus (of Meissner[2]).
- Myenteric or intermuscular plexus (of Auerbach[3]).

Each plexi contains a fine meshwork of neurons (ganglion, CD55 + ve) and supporting (glial, CD55 − ve) cells which control motility, absorption, secretion,

[1] Ondine—water nymph who cursed her unfaithful husband to breathe only while awake. As he fell asleep he died (German mythology).

[2] Georg Meissner (1829–1905)—German histologist, also described tactile corpuscles of the skin.

[3] Leopold Auerbach (1828–1897)—German neuropathologist.

and blood flow. Ganglion cells (nested in groups of four to six cells) receive extrinsic cholinergic and adrenergic signals.

- **Intrinsic** neuron stimulation causes muscle relaxation.
  (a) Nitric oxide (NO) is the prime mediator.
  (b) Other mediators include VIP, Histidine, substance P, Neurokinin A, Enkephalin, Gastrin Release Peptide, isoleucine, and many others.
- **Extrinsic**.
  (a) Cholinergic neurons (contraction).
  (b) Adrenergic neurons (relaxation).
- **Nonadrenergic and noncholinergic (NANC) nervous system.**
  – Controlled by interstitial cells of Cajal[4] also seem to play an important role in peristalsis.

23.4 Genetics

- Strong evidence of genetic predisposition.
  – The average risk of occurrence in siblings is 3–4% (↑ This risk is further increased in siblings of the individuals with long-segment disease involvement).
- **Gene mutations.**
  – The main gene responsible for increased susceptibility has been diagnosed as ***RET* gene,** which is a proto-oncogene playing a major role in the development of the enteric nervous system on Ch 10q11. Associated with Down's syndrome. Dominant mutations in RET gene have been found (50% familial and 15–35% of isolated cases).
  – Seven other candidate genes have been found to play a role in the pathogenesis of Hirschsprung's disease and these include ***SOX10, EDNRB*** (endothelin receptor type B), ***GDNF*** (glial cell line neurotrophic factor), ***EDN3*** (endothelin-3), ***ECE1, NTN, SIP1***.
- Mutations in any of these genes may lead to HD. In 50% of familial and 15–35% of isolated cases, dominant mutations in RET gene have been found.

23.5 Etiology

A number of hypotheses have been advanced to explain the lack of ganglion cells, including:

- **Failure of migration.**
  – Distal aganglionosis occurs in chick embryos, when the hindgut is transected.
  – Abnormal glycoproteins have been found in the distal aganglionic gut.

[4] Santiago Ramony Cajal (1852–1934)—Spanish pathologist and Nobel laureate.

- **Hostile environment.**
  - Loss of neural cell adhesion molecules (NCAM) leads to inability of normal ganglion cells to adhere to smooth muscle cells.
- **Immunologic attack.**
  - Abnormal immune response mounted by fetus against ganglion cells may lead to the destruction of ganglion cells.

23.6 Pathology

Lack of progression of peristaltic wave into the aganglionic segment of intestine and absent or abnormal internal anal sphincter relaxation is the hallmark of HD.

The gross appearance of the intestine varies with age of the child. In the neonatal period, the proximal intestine may appear normal but with the passage of time the proximal intestine distends and hypertrophies.

23.6.1 Variable Affected Segment

- **Short segment** (commonest).
  - Rectum and variable length of the sigmoid.
- **Long segment**.
  - Typically includes total colonic and a variable length of ileal involvement.
- **Total intestinal aganglionosis** (not compatible with life).
- **Ultra-short segment disease.**
  - Believed to be very rare and some even believe it to be non-existent.
- Similarly, **segmental disease or "skip" lesions** should not be considered in differential diagnosis due to rarity of the condition.

The affected aganglionic bowel looks normal, the ganglionic bowel looks abnormal.

23.7 Clinical Features

Two overlapping scenarios:

- Neonatal bowel obstruction.
  - Delayed passage of meconium, distension, bile vomiting ± enterocolitis (variable incidence).

N.B. 90% of otherwise normal term neonates will pass meconium within the first 24 h of life; and almost 95% will pass this within 48 h.

- Chronic constipation.
  - Enterocolitis (variable incidence).
  - Failure to thrive.
  - Encopresis (soiling) should be uncommon in HD.

Perforation may occur (~2%) as a complication of recto-sigmoid HD. Ileal perforation may complicate long-segment HD.

Explosive discharge of fecal matter or meconium may occur after rectal examination and is a valuable diagnostic sign. If this occurs following surgery it may indicate stasis and potentially enterocolitis.

23.7.1 Investigations

- *Abdominal XR*—multiple intestinal loops, absence of gas in the rectum.
- *Contrast enema* (Fig. 23.1)—ideally before the rectal examination. Looking for transitional zone. Delayed films may show contrast retention and are suggestive (Fig. 23.1)**.**
- *Submucosal rectal biopsy* (suction or occasionally open under GA).
  - 1 and 2 cm above the dentate line
  - ± Acetylcholinesterase staining (90% accurate, less so in neonates and LS HD)
  - ± Immunohistochemistry (e.g., LDH, S100, SDH, and Calretinin)
  - Pathologist dependent.

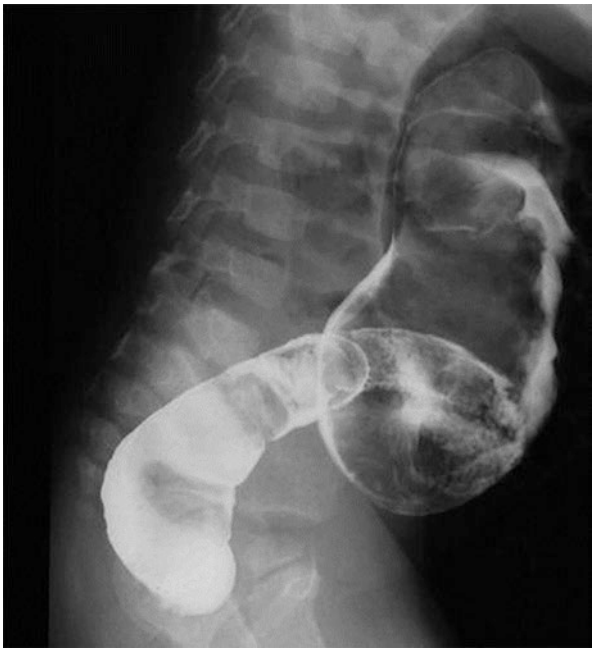

Fig. 23.1 Contrast study showing dilated proximal segment and distal narrow segment

- *Anorectal manometry*—relies on the absence of reflex relaxation of internal anal sphincter in response to rectal dilatation (Not widely available and operator dependent).

23.7.2 Differential Diagnosis

- Mechanical causes of neonatal bowel obstruction (e.g., ileal and colon atresia, anorectal malformations, meconium ileus, meconium plug syndrome (10% have HD)).
- Functional hypoperistalsis (e.g., prematurity, sepsis and electrolyte imbalance, small left colon syndrome, and hypothyroidism).

For the older child

- Idiopathic constipation, hypothyroidism, intestinal neuronal dysplasia, hyperganglionosis, etc.

23.8 Management

The aim always in HD is to decompress obstructed bowel and may be attempted even before definitive investigation.

If enterocolitis, a potentially lethal complication, is suspected (sepsis, pyrexia, diarrhea, bloody stool) then further active intervention is required including:

- Rectal washout.
  - 10–20 mL/kg of normal saline is instilled via a rectal tube in small volumes ensuring all fluid inserted is returned. Repeat up to 3× daily.
- Antibiotics (e.g., vancomycin and metronidazole).
- **± Colostomy/ileostomy**
  - Washouts may not be effective in LS disease and would be the commonest cause of "pathological" failure. Siting of the stoma is crucial and a frozen section should be available.

23.9 Surgery

Currently, following diagnostic confirmation most infants can be managed (by parents, at home) with daily rectal washouts until they are considered suitable for a single-stage primary pull-through procedure.

- *Colostomy (indications).*
  - Laparotomy for neonatal intestinal obstruction (in absence of diagnosis).
  - Low birth weight and preterm infants.

– Late diagnosis with hugely distended proximal bowel (especially in older children).
– Repeated episodes of enterocolitis (especially in LS disease).

Colostomy (transverse/sigmoid) or ileostomy (LS disease) should be performed in proximal, ganglionic (ideally confirm by frozen section) bowel. Use access to take serial seromuscular or full-thickness biopsies to confirm the level of disease in remainder of the colon.

23.9.1 Pull-Through Procedure

The aim is to resect the aganglionic segment, bringing the ganglionic bowel through the pelvis and anastomosing it near to the anal canal to allow unimpeded voluntary emptying. In historical order the commonest are:

- ***Swenson's[5] pull-through (1948).***
  (a) Removal of all aganglionic bowel up to 1 cm from dentate line posteriorly and 2 cm of dentate line anteriorly. Colo-anal anastomosis from outside.
  (b) Potential for pelvic nerve (incontinence) and anterior structure (vas, bladder, vagina) damage.
- ***Duhamel's[6] pull-through (1956).***
  (a) Dissection behind rectum (to minimize pelvic nerve damage) to create a tunnel. Ganglionic bowel is brought through ~1 cm above dentate and side-to-side anastomosis is created (with GIA or EndoGIA stapler).
  (b) Anterior blind pouch may lead to fecaloma and recurrent obstruction.
- ***Soave's endorectal pull-through[7] (1964).***
  (a) At pelvic reflection, the colon dissection continues in the submucosal plane to ~1 cm from dentate line. Ganglionic bowel is pulled through the rectal muscle sleeve and anastomosed to anal mucosa. Avoids potential for nerve damage.
  (b) Retained aganglionic muscle cuff may cause functional obstruction and constipation or sleeve abscess.
- ***Laparoscopy-assisted transanal pull-through.***
  (a) Any of the above can be performed under laparoscopic vision for the pelvic dissection.
- ***Transanal pull-through*** (Fig. 23.2)***.***
  (a) Using a circumferential (e.g., Scott) hook retractor, it is possible to dissect entirely from below (submucosa or full-thickness) into the peritoneal cavity, removing the aganglionic bowel and achieving a safe anastomosis.

[5] Orvar Swenson (1909–2012)—American pediatric surgeon, reached his 102nd birthday!

[6] Bernard Duhamel (1917–1996)—French surgeon, working in Hospital de Saint Denis, Paris.

[7] Franco Soave—Italian pediatric surgeon working in Genoa. As originally described the pull-through bowel was left hanging between the infant's legs and not actually anastomosed.

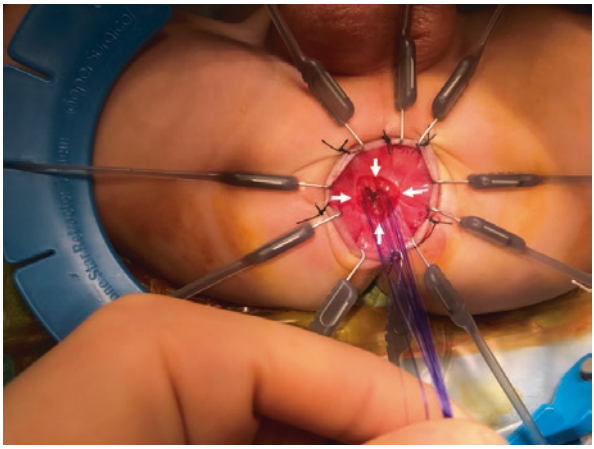

Fig. 23.2 Dissection starting on just proximal to the anorectal line as opposed to starting on the dentate line has recently been suggested to improve long-term outcomes. This (arrows) can be identified by hooking the crypts in the dentate line to expose the anal canal with a Scott retractor

23.10 Outcome

Early complications include enterocolitis, anastomotic leak and stricture, intestinal adhesion obstruction, and perianal excoriation.

The functional superiority of one of the above over another has not been shown in long-term follow-up series (although these are few). Nonetheless, in general, the Duhamel and Soave procedures seem to have a higher rate of constipation, while Swenson's may have a higher incidence of incontinence. Certainly, all patients need long-term follow-up as minor issues including the need for regular use of laxatives is not uncommon.

Further Reading

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