HIRSCHSPRUNG DISEASE

Epidemiology

HD is characterized by the absence of ganglion cells at the level of the submucosa and myenteric plexus (1). The disease involves the internal anal sphincter (IAS) and extends proximally affecting variable lengths of the intestine. The aganglionic segment is limited to the rectosigmoid in 80% of cases and extends proximal to the sigmoid in 20% where it may involve the entire colon (total colonic aganglionosis, 3-10%) or the proximal small bowel (less than 1%) (2-6).

The incidence of HD ranges from 1:5,000 to 1:10,000 live births (7, 8), with an estimated male to female ratio of 3:1 to 4:1 in rectosigmoid disease and 1:2 to 2:1 in left colon or more proximal disease (4, 9-11). Approximately 70% of children have isolated or non-syndromic HD and 30% are associated with chromosomal (12%) or congenital anomalies (18%) (7, 12, 13). Associated anomalies include Trisomy 21, Waardenburg-Shah syndrome, and congenital hypoventilation syndrome, amongst others (7, 14, 15). HD is a multigenetic disease with complex inheritance and variable phenotypic spectrum. Common and low frequency coding/regulatory variants in the RET, NRG1, and SEMA3C/D gene loci have been implicated in isolated, rectosigmoid HD, and sporadic forms of HD. In contrast, syndromic, total colonic aganglionosis/left colon or proximal disease, and familial forms of HD are observed with rare and high penetrant coding variants in a multitude of genes (16).

Clinical Presentation

Traditionally, HD has been considered a disease that primarily affects neonates with 80-90% of cases presenting in the first year of life (17). In a retrospective review of national in-patient databases, Aboagye et al reported that the mean and median ages of presentation were 3 year and 1 year, respectively (18). Symptoms vary based on age and extent of the aganglionic segment. In neonates, symptoms may range from delayed passage of meconium (>48 hours) and feeding intolerance to abdominal distention, bilious emesis, and intestinal obstruction. Conversely, infants and children may present with chronic constipation that is refractory to oral laxatives, is dependent on rectal therapy, and is associated with vomiting, abdominal distention, and failure to thrive (12, 19, 20). Hirschsprung-associated enterocolitis is the most recognized complication of HD with a mortality rate of 1-10% and may present preoperatively in up to 60% of patients (21-25). Symptoms include abdominal distention, fever, diarrhea (maybe bloody), vomiting, lethargy, and septic shock (24-26).

Diagnosis

Screening tests used in the diagnostic evaluation of HD are anorectal manometry (ARM) and contrast enema. Depending on the results, a rectal suction biopsy or full thickness biopsy is then performed to establish the diagnosis. In centers with manometric capability, ARM is recommended as the screening study of choice by European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and NASPGHAN (27). It is less invasive than a rectal biopsy and does not involve radiation exposure compared to contrast enema. In patients with HD, the recto-anal inhibitory reflex is absent (28, 29). Figure, Supplemental Digital Content 8, demonstrates the presence and absence of the recto-anal inhibitory reflex on high

resolution anorectal manometry. ARM has a sensitivity of 91% and specificity of 94%, compared to rectal biopsy at 93% and 98% respectively (30). False positives and negative results of ARM are largely technical and include air leak, displacement of the catheter, relaxation of the external anal sphincter (EAS), equipment problems, and insufficient inflation of the balloon (27, 31). These technical challenges maybe more pronounced in young infants especially given their small size and poor cooperation. In a systematic review, de Lorjin et al. reported lower diagnostic accuracy of ARM in infants younger than 6 months of age (sensitivity 88%, specificity 89%) (30). Despite its advantages, ARM requires technical expertise and knowledge and is not available in many pediatric gastroenterology centers (32).

Contrast enema is widely available in most pediatric centers, is less invasive compared to biopsy, but requires radiation exposure. The suggestive findings of HD include the presence of a transition zone, proximal bowel dilation, microcolon, irregular colonic contractions, irregularities in the mucosa and reversal of the rectosigmoid ratio (normal: r/s >1) (33-36). (Figure, Supplemental Digital Content 9). Diagnostic accuracy of contrast enema is variable with reported sensitivity of 70% and specificity of 83% when compared to ARM and rectal biopsy (30).

Histopathological confirmation is the gold standard for the diagnosis of HD (37). Depending on the center's expertise and the age of the patient, suction or full thickness rectal biopsy is performed. To date there are no recommended protocols or guidelines that delineate age and size cut off for suction and full thickness biopsies. The decision is primarily dependent on the surgeon and the institutional preferences. We would suggest a full thickness biopsy in patients older than 1 year of age to reduce the rates of insufficient sampling (38-40). Suction

biopsies are obtained at 1 and 2 cm, and if needed at 3cm, and 4 cm proximal to the anal verge using specialized rectal biopsy equipment. Samples are placed in formalin in separate containers and sent to pathology for evaluation. A full thickness biopsy is performed by a surgeon in the operating room under general anesthesia. To successfully establish or exclude the diagnosis of HD, the specimen should contain colonic mucosa with adequate submucosa. This is important in order to identify ganglion cells, the presence or absence of submucosal hypertrophic nerves (greater than 40 microns), and to perform ancillary testing including acetylcholinesterase enzyme (AChE) histochemistry and calretinin immunohistochemistry (IHC) (2). The absence of ganglion cells, the presence of hypertrophic submucosal nerves, and abnormal ancillary testing (absent calretinin-immunoreactive mucosal innervation or presence of AChE expression) is consistent with HD (2).

Surgical Management

The treatment for HD is pull-through surgery, with the goal of resecting the aganglionic segment of the rectum and colon and anastomosing the ganglionated bowel to the distal rectum close to the anus, while preserving the dentate line and the integrity of the anal sphincter complex. Several surgical techniques have been developed, with similar long-term results and complication rates (41, 42). The type of surgery depends on the surgeon's preference as well as the patient characteristics and pathological evaluation.

The operative plan may be one-stage, a primary pull-through procedure; two-stage, an initial diverting ostomy performed in the healthy colon followed by a pull-through; and three-stage, an ileostomy and colonic mapping as a first step followed by a pull-through at the

location where ganglion cells are found, and finally ileostomy closure. The decision on how to stage the pull-through depends on several factors including age and location of the transition zone. Patients less than 6 months of age and those with a transition zone in the left colon or more distal are usually able to undergo a one-stage procedure unless they have enterocolitis or malnutrition. Patients with a transition zone at the splenic flexure or more proximal need definitive pathology (not frozen section) to determine their level, thus those patients need colonic mapping and an ileostomy with a future pull-through. Older patients, who are diagnosed later in life and likely had chronic fecal retention, usually have dilated bowel that can make the pull-through operation technically challenging. These patients may at times benefit from a diverting ostomy (leveling colostomy or ileostomy) to allow for bowel decompression before proceeding with the pull-through. In a patient with severe enterocolitis already being addressed with standard supportive treatment including rectal irrigations and antibiotics, a diverting ostomy may be indicated to allow for clinical improvement before the pull-through. Patients with malnutrition are at risk for anastomotic complications, as well as patients with comorbidities, such as cardiac disease, who may benefit from a diverting ostomy. Patients whose pathology reveals total colonic aganglionosis undergo an initial ileostomy and subsequent pull-through of the ileum once good growth is confirmed and the stool has thickened.

There are three well described pull-through techniques: Swenson, Yancey/Soave, and Duhamel. The Swenson pull-through, first described in 1948, includes an intraabdominal (open approach or laparoscopic) and a transanal dissection (43). The dissection of the aganglionic segment in the Swenson pull-through is a radial full-thickness dissection that starts just

proximal to the dentate line, to which the proximal ganglionated segment is sutured end-to-end. Given the risks of injuring pelvic structures during the rectal dissection of the Swenson pull-through, the Soave or endorectal pull-through was described in 1964. Of note, the submucosal technique was first described by Yancey in 1952 in a less prominent journal (44). He has recently been recognized for this innovative technique. The approach avoids a perirectal dissection and instead creates a “cuff” of muscularis propria of the distal rectum (by dissecting submucosally at first) and then the pull through is passed within this cuff and anastomosed end-to-end with the distal rectum (45). Modifications to the Yancey/Soave procedure include decreasing the length of the aganglionic cuff and splitting the cuff posteriorly to decrease postoperative constipation and enterocolitis (46); laparoscopic and robotic assisted Yancey/Soave pull-through operations have been described as safe and effective techniques requiring a skilled minimally invasive surgical team (47). The Duhamel pull-through, prevents injuries to pelvic structures by avoiding the anterior rectal dissection so that the ganglionic bowel is anastomosed to the native posterior rectum in a side-to-side fashion. As expected with this approach, aganglionic bowel (the original rectum) is retained and can cause postoperative complications namely persistent constipation and recurrent enterocolitis.

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Tables and Figures:

Figure, Supplemental Digital Content 1. High-resolution anorectal manometry. A. Presence of recto-anal inhibitory reflex (RAIR). B. Absence of RAIR.

Figure, Supplement Digital Content 2. Contrast Enema (A) Normal rectosigmoid ratio of >1. (B) Abnormal rectosigmoid ratio of <1. (C) Arrow indicates uninhibited contractions (sawtooth mucosal pattern) in the affected region
r/s – rectosigmoid ratio