The Pathophysiology of Constipation

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Constipation is an extremely common disorder in childhood and is responsible for up to 25% of all pediatric gastroenterological consultations and 3% of all pediatric outpatient visits. In 90% of the cases the disorder is functional in origin and in only 10% is there an underlying organic disorder. Common organic causes of childhood constipation include: congenital defects of the gut; neurologic disease especially cerebral palsy, spinal cord disorders and hypotonia; endocrine and metabolic disorders (hypothyroidism, cystic fibrosis, hypercalcemia, diabetes mellitus, renal acidosis), and the use of constipating drugs such as some antacids, sucralfate, iron, codeine-containing medications, imipramine, phenytoin, etc. The commonest of the congenital defects is Hirschsprung’s disease, which has an incidence of 1 in 4,500 live births compared to 1 in 7,000 live births with anorectal malformations, and 1 in 40,000 with other enteric neuromuscular disorders. Fewer than 5% of children presenting for the first time with constipation have demonstrable organic disease.

Beyond the neonatal period, the most common cause of constipation is functional constipation, which has also been called idiopathic constipation, idiopathic megacolon or functional fecal retention. In children with functional constipation 40% develop symptoms during the first year of life. It usually begins at the time of toilet training or at school entry and is more prevalent in boys.
than in girls [2]. Childhood functional constipation differs significantly from constipation in adults. Fecal incontinence is more common in childhood constipation than in adults and is associated with withholding behavior in children and straining in adults. Treatment is more successful in children than in adults.

In this review the normal mechanisms of colonic transit and defecation followed by the known pathogenetic mechanisms resulting in constipation will be discussed.

**Normal Colonic Transit and Colonic Motility**

**Colonic Transit**

Transit of the luminal contents through the gut takes some 36–48 h in health. The time taken varies in different regions of the gut, being seconds to minutes in the esophagus, 30 min to 2 h in the stomach, and 1–4 h in the small intestine, the remainder of the time being spent in transit through the colon. Thus whole gut transit provides a good indication of colonic transit time. The colon is an organ of the gastrointestinal tract that is responsible for salvage of water, calories and electrolytes from the gut contents followed by excretion of the exhausted digesta. It is thus advantageous for the time that the luminal contents spend in the colon to be long. Several factors affect colonic motility, transit time and defecation frequency. A high fiber intake, extrovert personality, and male gender all correlate with a faster transit time and greater bowel frequency [3, 4].

A number of different methods have been used to measure colonic transit including scintiscanning of either stools or the abdomen or the measurement of the time a nonabsorbed marker takes to transit the whole gut. The latter methods using either radiopaque pellets or a dye such as carmine red, which can be readily seen in the stool, are those that are most readily used in clinical practice. Carmine red measures the time taken for the liquid phase to transit the gut and radiopaque pellets measure the solid phase. The method described by Metcalf et al. [5] is the one which is most useful, and easily detects rectal outlet obstruction, either due to functional withholding or due to disease affecting function of the anal sphincter, from slow transit constipation or colonic inertia. In brief, in this method radiopaque pellets of three different shapes are given orally on 3 successive days, a different shape on each day, and on the 4th day a plain abdominal X-ray is taken. The position of the different shapes in the colon is then determined. In health all the day-1 pellets should have been expelled. Using this type of method and a modified means of analysis, the time taken for digesta to transit the whole colon in normal children can be determined. There is a wide range which is similar in older children and adults of 30.7 ± 17.5 h. The time spent in the right colon, left colon and rectosigmoid has been estimated to be 8.9 ± 6.4, 8.7 ± 8.7 h and 13.0 ± 9.9 h, respectively, using radiopaque pellets and a segmental analysis method. In rectal outlet obstruction all of the pellets will be found in the rectum and in slow transit constipation the pellets will be distributed around the colon as shown in figure 1.

The gut luminal contents are propelled along the colon by its motor activity or motility. For most of the time colonic motor activity is characterized by quiescence or low amplitude segmenting contractions which are not coordinated between different regions of the colon [6]. These segmenting contractions mix the colonic contents, bringing the colonic contents into contact with the mucosa to facilitate absorption of water and epithelial nutrients such as acetate and butyrate. The segmenting contractions are responsible for the movement of colonic contents, in both antegrade and retrograde directions thus facilitating maximal exposure of the contents to the mucosa.

Several times each day a high pressure peristaltic wave develops which traverses a considerable length of the colon propelling the colonic contents before it. High amplitude peristaltic contractions (HAPCs) were first observed over 100 years ago in radiological studies of the colon in animals and humans by Cannon [7]. The peristaltic waves may arise at variable sites in the large bowel, from the cecum to the distal colon. They are the major motor event responsible for the transport of colonic contents. In a study of 14 healthy volunteers, colonic motor activity was monitored in the transverse, descending and sigmoid colon. HAPCs were easily identified by their characteristically high amplitude of <200 mm Hg, their duration of >10 s), propagation over at least 30 cm, and lack of overlap with other contractions [6]. In adults, HAPCs occur 4–6 times/day in a colon cleansed with cathartics [8, 9] and more infrequently (no more than 2/day) in a normal, unprepared colon [10]. In children, there is an age-related decrease in the frequency of HAPCs [11]. After a meal, the amplitude and frequency of segmenting contractions were seen to increase together with an increase in HAPC activity.

In addition to discrete contractile events, the colon exhibits variation in muscle tone which also increases after a meal and decreases during sleep [12]. The rectum also...
appears to have a distinct pattern of contractions, previously described as 'rectal motor complexes' [13, 14] which also increase after a meal.

**Normal Defecation**

The pattern of motor events occurring during defecation has perhaps surprisingly not been well studied. In one study in which defecation was induced by bisacodyl introduced into the left colon, high amplitude peristaltic waves were produced which proceeded distally together with a rise in rectal pressure. The internal anal sphincter relaxed simultaneously with the onset of peristalsis high in the left colon, and remained relaxed until the pressure wave reached the anus and the stool had been expelled. These findings suggest that the motor pattern required for defecation consists of colonic peristalsis, rectal contraction, and early anal relaxation. This coordinated pattern of motor activity is similar to the events which occur in the esophagus during swallow-induced peristalsis associated with early lower esophageal sphincter relaxation.

During defecation a variable amount of the colon is emptied depending on where in the colon the HAPC starts. The colon can empty from as much as the distal transverse colon to as little as just the rectum. When defecation is suppressed, retrograde movement of colonic contents occurs.

**Control of Colonic Motor Function**

The control of colonic motor function resides in the extrinsic nerves (cortical and spinal neurons), the intrinsic nerves within the colon, the interstitial cells of Cajal which act as pacemaking cells, and the properties of the smooth muscle cells of the colon themselves. Extrinsic...
innervation acts as a facilitator or inhibitor of colonic contractions. Although defecation is under cortical control, a major center for regulation is in the pons [15]. Studies in patients with spinal disease have suggested that within the spinal cord the pathway for control of defecation lies in the lateral column in close proximity to those pathways important for the control of micturition [16]. The intrinsic nerves of the myenteric and submucous plexuses coordinate sensory input from the colonic lumen and motor output and can be thought of as containing the ‘programs’ responsible for the patterns of contractile activity.

A specialized layer of pacemaking cells, the interstitial cells of Cajal, are present along the submucosal surface of the circular muscle, in the septal structures between muscle bundles of the circular muscle and associated with myenteric neurons [17]. These cells are critical for the propagation of slow waves, the organization of segmenting contractions and the frequency of HAPCs.

**Disturbed Colonic Motility in Constipation**

**Transit Studies**

Radiopaque markers to measure whole gut transit time as described above may be used to differentiate generalized colonic disease from outlet obstruction. In functional constipation, the markers are usually found in the rectum within 36 h. In slow transit constipation or colonic neuromuscular diseases, the markers are scattered throughout the colon for many days with a whole gut transit time in excess of 84 h. When that happens, full thickness biopsies or colonic manometry studies can differentiate between neuropathy and myopathy.

**Patterns of Disturbed Motility**

**Colonic Motility**

Early studies of colonic motility in constipated patients often involved only the distal colon and were of short duration. They demonstrated increased segmenting activity.

In severe idiopathic constipation, the most important abnormality of colonic motor activity, however, is a decrease in the frequency and duration of mass movements. In one study mass movements were investigated in 14 chronically constipated women using a colonoscopically inserted manometric tube [18]. Patients demonstrated a mean of 2.6 mass movements in 24 h, compared with a mean of 6.1 in controls. An absence of mass movements during the 24 h was observed in 4 patients but in none of the controls. Mass movements were decreased in duration in patients from a mean of 14.1 to 8.2 s. In patients the mass movements therefore progressed a lesser distance along the colon, as the speed of propagation was the same in both groups (1 cm/s).

The colonic response to eating is also impaired in patients with severe constipation. The colonic response to a standard meal was studied in 15 patients with slow transit constipation and 29 healthy volunteers [9]. After ingestion of a meal patients exhibited a shorter duration of contractile activity and less high amplitude propagated contractions in the transverse, descending and sigmoid colons compared with healthy subjects.

Although patients with severe idiopathic constipation demonstrate a decrease in the frequency of HAPCs, it appears that the neural program for peristalsis and the colonic ability to contract are intact. In a study of colonic peristalsis in women with severe constipation, frequent HAPCs were induced using stimulant bisacodyl [19]. HAPCs progressed distally to induce rectal contraction, anal relaxation and effective evacuation, similar to that which occurs in healthy subjects [20].

In functional constipation, colonic motility is normal with the presence of HAPCs following awakening or a meal, and there is an increase in the motility index after a meal. A decreased frequency of HAPCs has been reported in adults with colonic inertia [9] and in children with neuropathies involving the colon [21]. Prolonged studies of colon motility coupled with small bowel recordings have been used to predict the success of surgery in adults with severe constipation [22, 23]. Colonic manometry may identify the segment of colon with abnormal motor function and also provides insights in the decision of whether to reconnect a diverted colon. The treatment of choice in infants with symptoms suggestive of colonic pseudo-obstruction is to place a decompression ileostomy. Once the child has grown and the symptoms have improved, the decision to reconnect the colon can be based on the results of motility studies of the diverted colon and knowledge of the activity of the underlying enteric neuromuscular disease [24, 25]. Colonic manometry is also helpful in clarifying the mechanism of fecal incontinence in children who have undergone surgery for Hirschsprung’s disease and present with soiling despite good anal sphincter function. Repetitive HAPCs which propagate to the neo-rectum just above the anal sphincters (instead of stopping above the pelvic floor) may overcome the resistance produced by the in-
ternal and external anal sphincter and produce involuntary passage of stools.

In colonic neuromuscular diseases, in the absence of generalized colonic dilatation, children whose contractions do not increase following a meal and/or who do not produce HAPCs may have a colonic neuropathy or an inflammatory disorder of the colon which is also involving the neuromusculature. Children with complete absence of colonic contractions are more likely to have a myopathy usually associated with a dilated colon.

Anorectal Motility
Anorectal manometry has been used extensively to diagnose Hirschsprung’s disease and to study functional constipation. In Hirschsprung’s disease, the lack of the rectoanl inhibitory reflex upon rectal distension has been considered diagnostic but there is a sizable subgroup of children with pseudo-Hirschsprung’s disease in which the rectoanl inhibitory reflex is abnormal or even absent, demonstrating that anorectal manometry is not specific for Hirschsprung’s disease and that for firm diagnosis a suction or full-thickness rectal biopsy is crucial. Studies of functional constipation are conflicting and often it is unclear if the manometric abnormalities represent a primary disorder or are secondary to the chronic fecal retention and voluntary withholding [26].

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Etiology of Abnormal Motility
Disturbances of colonic and anorectal motility are likely to have different mechanisms in different types of constipation. In patients with a megarectum or megacolon, defective muscle contraction will be present, but in less than 10% of children this will be due to organic disease affecting the colonic neuromusculature [1].

Functional Constipation
In the majority of children constipation will be functional in origin. Infants may fail to pass stools because of inadequate water or feeding intake. As the colon conserves water stools become hard and difficult to pass and as a consequence defecation is inhibited. Sometimes, breastfed babies do not pass stools for several days due to a marked decrease in unabsorbable residue. In these cases, the addition of fruit juices to the diet and an increase in fluid intake is sufficient to make the stool softer and increase the frequency of bowel movements.

When the parents overreact to the child’s struggle to defecate, the parental anxiety associated with each attempt becomes disturbing for the child. The child may respond to the urge to defecate with attempts to withhold, contracting the anal sphincter and the gluteal muscles to avoid defecation. The rectum accommodates to the fecal mass and the urge to defecate passes. With the passage of time, such behavior becomes an automatic learnt response. Passing a very large stool which painfully stretches the anal sphincter provides reinforcement that defecation should be avoided. As the rectum wall dilates the anal sphincter relaxes inappropriately and fecal soiling may occur, angering the parents and frightening the child. A number of other factors also play a role. Attempts to accomplish toilet training at an inappropriately early age (<2.5 years of age) and excessive pressure to achieve a perfect daily defecation trigger a power struggle between parents and child causing the child to withhold their stools on the rectum. Initial entry to school is another period when difficulties with defecation may also start due to separation anxieties and the unwelcoming state of school lavatories. Distraction by playing with friends or watching television may persuade children to postpone defecation repeatedly, thus inducing constipation [2].

Extrinsic Nervous Disorders
Neurological disease, either centrally in the brain or in the spinal innervation, is perhaps the next commonest cause of disordered defecation. The colon appears to depend on its extrinsic nerve supply to maintain normal function, with the distal colon receiving direct innervation from the S2–S4 roots [27]. Neurological disease is underestimated in both adults and children. A review of 31 million discharge diagnoses in elderly adults found that the largest group of constipation-associated diseases concerned neurological and psychiatric diseases [28]. Although similar data are not available in children, pediatricians commonly deal with such problems in children. Such children represent a very heterogeneous population with different mechanisms important in different groups of children. In tube-fed children, the lack of dietary fiber results in hard stools. The absence of normal skeletal muscle tone and coordination will result in feeble defecatory effort. Drugs commonly used in children with neurological disease, such as opiates, anticonvulsants and drugs with anticholinergic properties, cause additional impairment of colonic motility. A study of children with cerebral palsy showed delayed transit in the left colon of those constipated [29]. Colonic and...
rectal motility are modulated by extrinsic nerves consisting both of parasympathetic and sympathetic nerves fibers. The proximal colon receives cholinergic innervation from the vagus and the distal colon receives cholinergic input from the sacral pelvic nerves (S2–S4 roots) [27]. The splanchnic nerves, with nerve bodies in the superior mesenteric ganglion, provide adrenergic innervation to the proximal colon, and the lumbar nerves, with nerve bodies in the inferior mesenteric ganglia, provide innervation to the distal colon. Damage to the extrinsic nerves and thus loss of inhibitory input to the gut results in abnormal colonic and anorectal motility. In children with spinal cord injury or dysraphism, there is loss of the gastrocolonic response, the rectoanal inhibitory reflex is usually preserved but the external sphincter is often paralytic and the urge for defecation may be lost. As a consequence, children with myelomeningocele may have both constipation and fecal incontinence [30].

Intrinsic Neuromuscular Disease

Less than 10% of children with constipation have a disease which is either congenital or acquired that affects the enteric neuromusculature [1]. The commonest of the congenital defects is Hirschsprung’s disease which has an incidence of 1 in 4,500 live births compared to 1 in 7,000 live births with anorectal malformations, and 1 in 40,000 with other enteric neuromuscular disorders. It is beyond the scope of this article to review the many different neuromuscular diseases and interested readers are referred to a recent review [31].

Acquired diseases are nearly always inflammatory in origin and may present with either severe intractable constipation or recurrent episodes of pseudo-obstruction [32, 33]. Often autoimmune mechanisms are present and respond to immunosuppressive treatment [32, 34]. In others, especially those who are atopic, the constipation may be secondary to food allergy [35].

It has also become recognized that alterations in the environment of the neuromusculature, either by inflammatory disorders or the circulating hormonal environment, may have a direct effect on colonic function. Steroid hormones have been examined in young women with severe idiopathic constipation [36]. Hormones were compared in the follicular and luteal phases in 23 healthy women and 26 patients with idiopathic constipation. The patients with constipation had a consistent reduction in the concentration of most of the steroid hormones in both phases of the cycle, and no abnormality in the pituitary hormones or sex hormone-binding globulin. No such studies have been undertaken in constipated adolescent girls but there is no reason to believe that the findings would be different.

Circulating gastrointestinal hormones have also been assessed in patients with severe idiopathic slow transit constipation [37]. The hormone response to a standard meal was assessed in 12 women with constipation and 12 controls. Somatostatin was elevated in the constipated women; whether this is a primary or secondary abnormality has not been elucidated.

References


