Unraveling childhood constipation: Pathophysiology, diagnostics and treatment

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GENERAL INTRODUCTION

OUTLINE OF THIS THESIS

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GENERAL INTRODUCTION

Epidemiology
Constipation represents a common problem in children, accounting for 3-10% of visits to general pediatric clinics and up to 25% of referrals to pediatric gastroenterologists. The worldwide prevalence of functional constipation in children varies from 0.7% to 29.6%, with this condition occurring in all pediatric age groups, from newborns to young adults. The wide range in reported prevalence may be due to the use of different criteria to define functional constipation and to differing cultural influences about what is considered a normal bowel habit. Peak incidence occurs at the time of toilet training, with no consistent effect of gender on its prevalence.

Definition of constipation
From the age of 3 years, normal stool frequency varies from three stools per week to three stools per day. Between 5 years and 8 years of age, the majority of children have a medium-size bowel movement daily or every other day without straining or withholding. For many years, physicians, patients and parents used different definitions for constipation. The Rome II criteria (developed in 1999) attempted to provide a symptom-based definition of functional childhood constipation, mostly based on expert opinion. Such criteria were subsequently found to be too restrictive and were revised (between 2004 and 2006) in the Rome III version of pediatric functional gastrointestinal disorders. To fulfill the new Rome III criteria for functional constipation, children should have two or more of the symptoms depicted in Table 1. These changes in diagnostic criteria have resulted in 42% more children being diagnosed with functional constipation.

Table 1. The Rome III criteria for pediatric functional constipation

<table>
<thead>
<tr>
<th>Two or more criteria for at least 2 months prior to diagnosis in a child with a developmental age of at least 4 years</th>
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<tr>
<td>- Two or fewer defecations per week</td>
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<td>- At least one episode of fecal incontinence per week</td>
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<td>- Stool retentive posturing</td>
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<td>- Painful or hard bowel movements</td>
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<td>- Large diameter stools which may obstruct the toilet</td>
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<td>- Presence of a large fecal mass in the abdomen or rectum</td>
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Quality of life
Children with functional constipation report impaired Health-Related Quality of Life (HRQoL) in relation to physical complaints and long duration of symptoms. In about one third of children with constipation, symptoms continue into adulthood. When childhood constipation continues into adulthood, it influences HRQoL negatively with social consequences in 20% of these adults. Constipation is often associated with fecal incontinence, which is a source of considerable embarrassment for children, who must often deal with taunting by peers and punishment from frustrated parents. As a consequence, low self-esteem, depression, social withdrawal, shame, fear of discovery
and anger ensue. In a 2011 Dutch study, it was reported that the prevalence of behavioral problems in children with functional constipation was threefold to fourfold higher than in a general pediatric population, and that the frequency of fecal incontinence was associated with externalizing problems, including delinquent and aggressive behavior. Substantially higher rates of oppositional behavior were reported by parents of children with a frequency of fecal incontinence episodes of more than one per week. Unfortunately, data regarding behavioral problems in children with constipation treated in primary care are lacking.

Healthcare costs
Because of its wide prevalence and chronic nature, constipation is a significant source of health care expenses. An analysis of three national surveys in the United States estimated the constipation-related health care costs in adults to be about $235 million in 2001. Mean annual costs for treatment of chronic constipation were calculated $7,522 per patient and average costs of diagnostic work-up have been shown to approach $3,000 per patient. A 2011 population-based longitudinal study on the costs related to constipation over a 15-year timeframe reported that children with constipation from childhood to early adulthood had more visits to outpatient clinics and emergency department and more inpatient hospitalizations than matched controls. Another study performed in the USA, using the Medical Expenditure Panel Survey database, estimated that childhood constipation results in an additional cost of $3.9 billion per year.

Pathophysiology
The pathophysiology of constipation in children is multi-factorial and remains incompletely understood. In a fraction of patients, constipation is secondary to a known organic disorder, such as anorectal malformations, Hirschsprung’s disease, neurological abnormalities, or an endocrine or metabolic disorder. In > 90% of children presenting with constipation, no obvious organic cause is found and a diagnosis of functional constipation is made. The most common etiology of functional constipation is withholding of stools, starting after an experience of a hard, painful, or frightening bowel movement. As a consequence of the withholding, the rectal mucosa absorbs water from the fecal mass, and the retained stools become progressively more difficult to evacuate. This leads to a vicious circle of stool retention in which the rectum is increasingly distended, resulting in overflow fecal incontinence, loss of rectal sensation and, ultimately, loss of normal urge to defecate. An association has been found between early constipation and difficulties with toilet training.

Megarectum
The rectum is central to the process of defecation. It has been reported that some children with chronic constipation may have an increased rectal compliance, reduced rectal sensation or both. Accordingly, abnormalities of rectal wall properties and/or sensorimotor dysfunction may conceivably lead to problems with evacuation. Whether the sensorimotor dysfunctions are primary or secondary to constipation is currently unknown.
Slow transit constipation
A delay in total and segmental colonic transit time has been described in a subgroup of children with chronic constipation.24–26 This delay might be due to dysfunction of the muscles of the colonic wall (resulting in non-powerful peristaltic contractions) or to dysfunction of the enteric nervous system (resulting in noncoordinated motor activity).27 In children, however, it might also be possible that delay in colonic transit time is secondary to the massive chronic fecal retention in the rectum.3 A reduction in the number and delayed maturation of interstitial cells of Cajal (ICCs) has also been suggested to have a role in the pathophysiology of slow transit constipation in children.28–30 Reduction of ICCs is the most consistent histological finding in slow transit constipation to date, although little is known about ICC numbers in healthy children.31 Whether the ICC changes are primary or secondary to chronic constipation is also unclear. Given the important role of ICCs in the control of motility (as pacemaker cells that generate gut peristalsis), it has been argued that any abnormality in the ICCs may be clinically significant.32 Abnormalities in the expression, density, and/or function of substance P and vasoactive intestinal peptide in the colonic circular muscle of children with constipation have been identified in several studies by immunohistochemistry.32–35 These histological findings correlated with a delayed colonic transit time in patients with childhood constipation.33

Genetics
Genetic predisposition may play a role in the development of childhood constipation, as constipation often dates back to the first months of life and many patients have a positive family history of constipation.34,36,37 A 2011 systematic review showed that genetic factors do indeed have a role, but mutations in genes specifically associated with constipation have yet to be found. Presence of a clinical syndrome should be investigated in familial cases of childhood constipation, because there are numerous of syndromes associated with chronic constipation.38

Brain processing
Brain processing of visceral sensation is complex and comprises sensory, affect and cognitive components.39 The bi-directional communication between the gut and the central nervous system is called the brain-gut-axis and is increasingly recognized as important in functional gastrointestinal disorders (Figure 1).40 Increasing studies have been conducted to unravel the brain processing of visceral sensation in adults with functional gastrointestinal disorders using functional brain imaging techniques. Brain-imaging literature hypothesizes an abnormal brain-gut communication or abnormalities in signal processing of enteric nervous system as a cause for functional GI disorders in adults.41 Brain imaging studies are still in their infancy in pediatrics, and no information is available about central nervous system activation in children with functional gastrointestinal disorders.42
**Associated factors**

Several environmental and social circumstances have been associated with a higher prevalence of childhood constipation, including low consumption of fiber, positive family history, obesity and low level of physical activity, living in a highly-densely populated community and low parental education level.\textsuperscript{2,4,44} The relationship between behavioral problems and constipation is complex, in part because constipation can be both a cause and a consequence of behavioral problems.\textsuperscript{13} Constipation has been reported more frequently in children with specific behavioral phenotypes such as autism spectrum disorder.\textsuperscript{45}

![Figure 1. Cortical modulation of homeostatic afferent input to the central nervous system. Prefrontal regions modulate activity in limbic and paralimbic regions, subregions of the anterior cingulate cortex, and hypothalamus, which in turn regulate activity of descending inhibitory and facilitatory descending pathways through the periaqueductal gray and pontomedullary nuclei. Activity in these corticolimbic pontine networks mediates the effect of cognitions and emotions on the perception of homeostatic feelings, including visceral pain and discomfort. Abbreviations: dIPFC = dorsolateral prefrontal cortex; orbFC = orbitofrontal cortex; PAG = periaqueductal gray; RVM = rostroventral medulla; A6, locus coeruleus; Ins = insula; Hypoth = hypothalamus; Amy = amygdala; ACC = anterior cingulate cortex. Reprinted with permission from Annual Reviews.\textsuperscript{46}](image-url)
Clinical evaluation and diagnostic testing

In over 95% of children presenting with constipation a diagnosis functional constipation is made. A thorough history and physical examination are essential and usually sufficient to rule out most organic causes of constipation. In general, it is not necessary to perform any testing before initiating treatment. Only in atypical cases with warning features (Table 2) or when there is no improvement with conventional therapy further testing is indicated.

Medical history

An assessment of the stool pattern, using a defecation diary in combination with the Bristol stool scale or Amsterdam infant stool scale, can be used to estimate the severity of constipation. Knowledge of the time of the first bowel movement is important to discriminate functional constipation from Hirschsprung’s disease. Other important factors to investigate include the frequency, consistency and size of stools; whether the child experiences pain during defecation, presence and timing of fecal incontinence, stool withholding behavior, and presence of blood on the stool or the toilet paper. The involuntary leakage of feces may occur several times a day and, in the presence of a large rectal impaction, it can also occur at night. Stool-withholding behavior is reported in high percentages of constipated children. Parents describe that their children hold their legs and buttocks stiffly together, rise on their toes and then rock back and forth. In many cases, parents misinterpret this behavior as an extreme effort to pass stool. Patients should be asked about accompanying symptoms such as abdominal pain, loss of appetite, urinary tract problems, fever, nausea, vomiting, weight loss or poor weight gain, problems in neuromuscular development, and psychological or behavioral problems. Dietary history and the history of previous treatment strategies for constipation should be investigated. Finally, enquiries into important life events, such as death in the family, birth of a sibling, school problems and sexual abuse, which might contribute to the development of retentive behavior, are essential. Alarm symptoms that might be related to sexual abuse or organic causes of constipation are summarized in Table 2.

Table 2. Warning symptoms of organic causes and sexual abuse

<table>
<thead>
<tr>
<th>Organic causes:</th>
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<tbody>
<tr>
<td>1. History: Passage of meconium &gt; 48 hours after birth, bloody diarrhea, fatigue, fever, bilious vomiting, eczema</td>
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<tr>
<td>2. Physical exam: failure to thrive, fever, abdominal distension, peri-anal fistula, abnormal position of anus, absent anal wink, absent cremasteric reflex, decreased lower extremity strength/tone/ reflex, tuft of hair on spine, sacral dimple, spina bifida</td>
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</table>

<table>
<thead>
<tr>
<th>Sexual abuse:</th>
<th></th>
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<tbody>
<tr>
<td>1. History: smearing feces</td>
<td></td>
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<tr>
<td>2. Physical exam: extreme fear during anal inspection or rectal exam, anal scars, fissures, hematomas.</td>
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</tbody>
</table>
General Introduction

Physical examination
The physical examination should include a thorough abdominal examination, perianal inspection and anorectal digital examination. Abdominal examination gives valuable information concerning accumulation of gas or feces. Perianal inspection provides information about the position of the anus, perianal feces, dermatitis, eczema, fissures, hemorrhoids and occasionally scars as sequelae of sexual abuse. Abnormalities such as gluteal cleft deviation may suggest the presence of lumbosacral spine abnormalities. The anorectal digital examination assesses perianal sensation, anal tone, size of the rectum, amount and consistency of stool in the rectum, contraction and relaxation of the anal sphincter and presence of an anal wink.

Laboratory tests
In general, laboratory investigation of constipated children rarely uncovers an underlying disease. If indicated, laboratory tests should include serologic assays for celiac disease and evaluation of thyroid function.

Radiological tests
Radiological tests have only limited clinical value in the diagnosis of childhood constipation. A plain abdominal X-ray is inexpensive and frequently used, but a poor diagnostic association has been suggested between clinical symptoms and fecal loading on a radiograph. An MRI of the spine is indicated in children with intractable defecation disorders presenting with neurological complaints and/or physical symptoms, suggestive of spinal cord abnormalities. A barium enema may be useful to identify anatomic abnormalities and detecting Hirschsprung’s disease. However, there are limited studies evaluating clinical utility. Defecography is a dynamic radiologic study that enables imaging during voluntary evacuation of the rectum. It gives information regarding the anatomical and functional changes of the anorectum.

Colonic transit time
There are several methods to evaluate gastrointestinal motility and measure colon transit time. The use of sitz markers is non-invasive, inexpensive and widely available. Colonic transit can be easily measured by the ingestion of radiopaque markers followed by abdominal radiographs (Figure 2). It is a useful tool to differentiate between children with constipation and children with functional non-retentive fecal incontinence (FNRFI). Colonic scintigraphy and the wireless motility capsule (WMC) are newer techniques to assess colonic transit. Scintigraphy involves measuring the movement of a capsule containing an isotope (111In of 99Tc), on gamma-camera images. The WMC is an ambulatory technique, which measures intraluminal pressure, temperature and pH in the GI tract. Colonic scintigraphy and WMC are more costly and not widely available. The clinical usefulness of both techniques has to be explored in children and they are still considered a research tool in pediatrics.
Barostat
Barostat comprises of a highly compliant balloon that is placed in the rectum and connected to a computerized pressure-distending device. It can be used to measure rectal tone, compliance, and sensation by inflating air when outside pressure falls and to aspirate air when the pressure rises.48

Manometry
Anorectal manometry
Anorectal manometry is a largely safe and noninvasive technique. It measures pressures in the anorectal region and investigates the function of the internal and external anal sphincters.57 Anorectal manometry is only indicated to demonstrate the presence of the recto-anal inhibitory reflex, which is absent in children with Hirschsprung’s disease or in children with anal achalasia or ultrashort segment Hirschsprung’s disease.48,58 When the recto–anal inhibitory reflex is absent, the diagnosis of Hirschsprung’s disease has to be confirmed by histochemical evaluation of the rectum, which shows absence of ganglion cells in the submucosal and myenteric plexus.

Figure 2. An abnormal colonic transit study of a constipated patient. The abdominal X-ray shows large amount of stool and retention of markers throughout the entire colon.
Colonic manometry

Colonic manometry enables measurement of colonic motor activity. The test is performed in specialized motility centers to differentiate between normal colonic motor function and colonic neuromuscular disorders. Changes in the intracolonic pressure due to lumen-occluding contractions are measured during the test. High amplitude propagating contractions (HAPCs) are the most recognizable feature observed during a colonic manometry and together with a gastrocolonic response to a meal it is a marker for normal colonic motility. This test is used in clinical practice to identify children who may benefit from surgery, such as the creation of an antegrade continence enema.\textsuperscript{15,60}

Treatment

Treatment of childhood constipation consists of a four-step approach involving education, disimpaction, prevention of re-accumulation of feces and behavioral therapy.\textsuperscript{46} Education and support for parents and children is an important component of treatment of functional constipation. The parents need to be counseled regarding normal frequency of bowel movements, the prevalence and etiology of constipation, and the prognosis. If fecal incontinence is present, it is important for parents to understand that this is caused by overflow diarrhea and is not an act of willful behavior. Therefore is a positive approach, with sometimes a rewarding system, to motivate their children very important. Completing a bowel diary and a toilet training for children above the developmental age of 4 years (3 times a day trying to defecate on the toilet for 5 minutes) are important parts of the treatment.

Disimpaction

Approximately 30% of children with long-lasting functional constipation present with abdominal and/or rectal fecal impaction, which results in severe fecal incontinence in 90% of the patients.\textsuperscript{61} Children who undergo disimpaction are more likely to respond successfully to maintenance treatment.\textsuperscript{62} Fecal disimpaction can be accomplished with oral, nasogastric or rectal agents. The efficacy and safety of orally administered polyethylene glycol (PEG) has been studied in several trials. Successful disimpaction occurred in 75% - 92% of the children after 3 to 6 consecutive days, with a most effective dose of 1.0 to 1.5 g/kg per day.\textsuperscript{63,64} All studies have shown that PEG with or without electrolytes is safe to administer and all adverse effects associated with PEG seem to be related to its osmotic laxative effect. Two pediatric studies compared the efficacy of different disimpaction regimens. Guest et al. showed that oral PEG with electrolytes is significantly more effective for disimpaction than suppositories and rectal enemas or manual evacuation.\textsuperscript{65} By contrast, Bekkali et al. showed in a prospective randomized controlled trial (RCT) that high dose of PEG orally is equally effective as enemas for fecal disimpaction.\textsuperscript{66}
Maintenance treatment
Once disimpaction has been accomplished, the goal is to produce regular soft, painless bowel movements. Regularity for a longer period of time is important to prevent recurrent impaction and recurrence of stool withholding behavior. This approach usually requires maintenance laxatives in combination with behavioral therapy over a period that can last for months or years. Dietary modifications and laxatives as maintenance treatment for constipation have been extensively investigated in adults, but pediatric data are limited. Placebo-controlled trials showing the effectiveness and safety of maintenance therapy over placebo in children with constipation are lacking. Still, the use of laxatives in clinical pediatric practice is widely accepted. Disappointingly, only 50% of all children followed for 6 to 12 months completely recover from constipation and are successfully taken off laxatives.

Dietary interventions
Fiber
Conflicting evidence in the literature exists regarding the role of dietary fiber in the etiology and treatment of childhood constipation. The recommended minimum daily fiber intake for children older than 2 years is age in years plus 5 g. Several studies have indicated that children with constipation have a significant lower fiber intake compared to healthy controls, but others have not supported this finding. The protective role of fiber against constipation is supposedly related to its ability to induce osmotic (by increasing fecal volume and softening the stool by increasing bacterial mass) and mechanical stimulation (pro-motility effects of products of bacterial fermentation) of colonic motility. However, inconsistent data exist about the role of fiber in shortening colonic transit time. Therefore a balanced diet containing whole grains, fruits, and vegetables is recommended as part of the treatment of constipation, without forceful implementation of fiber in the diet.

Fluids
Increased fluid intake is a widely recommended therapy and is based on the assumption that additional oral intake of fluids leads to an increased contribution to colonic fluids, which would enhance increased stool output. However, literature shows no change in bowel habits after increasing daily fluid intake. This might be due to the large absorptive capacity of the small and large bowel. The lack of evidence that constipation can be treated by increasing fluid intake, leads to the suggestion that constipated children should not be forced to drink more than normal.

Probiotics
Probiotics are being increasingly evaluated as a treatment option in the management of childhood constipation. Mechanisms of action by which probiotics might be beneficial have not been fully elucidated. One hypothesis is that dysbiosis occurs in the gut flora of constipated patients, which might improve after ingestion of probiotics. However, whether this dysbiosis is a secondary manifestation of constipation or a factor that contributes
Another suggestion is that probiotics might decrease colonic transit time, due to a reduction in pH of the colon. Despite these hypotheses, a 2010 systematic review reasoned that no conclusive evidence exists that probiotics are effective in the treatment of pediatric functional constipation. These conclusions were not changed by a 2011 large double-blind RCT that investigated the efficacy of the *Bifidobacterium lactis* strain DN-173 010 in childhood constipation. Although treatment with the probiotic strain did increase stool frequency this increase was comparable in the control group.

**Oral laxatives**

Available oral laxatives consist of osmotic (e.g. lactulose, PEG) and stimulant (e.g. bisacodyl, senna) laxatives. Osmotic laxatives retain water in the intestinal lumen, which leads to softer stools with a larger volume and improved propulsion. Stimulant laxatives act on the enteric nervous system to increase intestinal motility and increase secretion of fluids and electrolytes. Only two randomized controlled trials have been performed to compare oral laxatives versus placebo for childhood constipation. Both studies used PEG3350 and showed that this compound was more effective than placebo in increasing the number of bowel movements and reducing the number of hard stools, pain and straining during defecation. Several RCTs have been carried out comparing PEG to lactulose. All these trials have used different inclusion criteria, outcome measures, dosages and study designs, making it difficult to draw firm conclusions. A 2010 Cochrane review concluded that PEG is superior to lactulose for the outcomes of stool frequency per week, form of stool, relief of abdominal pain and the need for additional products. Clearly, more studies in constipated children in primary, secondary and tertiary care, are necessary to determine and understand the role of the different laxatives available. These studies should not only compare these compounds against placebo, but should also evaluate the role of stimulant laxatives in combination with osmotic laxatives.

**Behavioral therapy**

Behavioral interventions, in combination with laxatives aim to reduce the level of emotional distress and to restore normal bowel habits by positive reinforcement. The effects of behavioral and/or cognitive interventions were assessed for the treatment of functional constipation in children. There is some evidence in the literature showing that behavioral interventions plus laxative therapy, rather than behavioral interventions or laxative therapy alone, improves continence. However, the advice was that psychological referral is only indicated in constipated children with severe emotional problems, scored upon validated child behavioral checklists.

**Enemas**

It is well known that retrograde enemas are therapeutically effective in the treatment of children with a neurological disorder, including spina bifida, but little knowledge exists about the role of retrograde enemas in the maintenance treatment of children.
with chronic functional constipation. A 2009 RTC showed that application of enemas on a regular basis is well-tolerated in children, but had no additional benefit over conventional treatment with oral laxatives in the maintenance phase of treatment.\textsuperscript{94}

**New therapies**

Several new therapies have been suggested for the treatment of constipation in adults. Increasing insight in the physiology of the intestinal nervous system, has led to the development of new classes of drugs for constipation. These drugs often target a specific receptor, which is known to affect intestinal function. Based on their mode of action, these drugs can be divided into different classes – 5-HT4 receptor agonists (e.g. prucalopride), chloride channel activators (e.g. lubiprostone), opioid antagonists, and neurotrophins.\textsuperscript{84,95} With all of these agents, pediatric data are lacking and further studies are required that assess safety, efficacy, and tolerability.

**Surgery**

The majority of children with functional constipation are successfully treated with conventional medical therapy. However, a small group of patients have severe, refractory symptoms, unresponsive to intensive medical management. This particular minority may benefit from surgical interventions.

**Antegrade enemas**

The use of antegrade continence enema (ACE) has been reported as a successful therapeutic option for patients with long-lasting constipation when maximal conventional therapy is not successful. The antegrade delivery of cleansing solutions enables the patient to evacuate the colon at regular intervals, avoiding impaction of feces and reducing fecal incontinence. Since Malone first reported administration of ACE through an appendicostomy, many modifications have been made, with most recent the percutaneously inserted cecostomy button.\textsuperscript{96,97} The use of ACE in children with functional constipation has proven to be effective, but success rates vary between 52\% and 92\% among the different studies.\textsuperscript{98–101} All studies agree that the use of ACE leads to an improvement in the number of bowel movements per week, number of incontinence episodes and quality of life scores.\textsuperscript{102,103} Complications include development of granulation tissue, leakage around the tube, tube dislodgment, skin infection, and stoma stenosis.

**Rectosigmoid resection**

Little experience exists about the role of rectosigmoid resection in children with functional constipation. Levitt et al. performed a transanal rectosigmoid resection with a primary colo-anal anastomosis in 15 children.\textsuperscript{104} All patients had an extreme dilated and hypomotile rectosigmoid with a normal-caliber descending colon. A concern with this procedure is the potential loss of rectal reservoir that may cause postoperative fecal incontinence.
General Introduction

Neuromodulation
Neuromodulation is a novel therapy for patients with severe constipation. The mechanism of action involves direct stimulation of sacral nerves and requires percutaneous placement of an electrode in the third sacral foramen and implantation of a stimulating device under the skin in the buttocks. Sacral neuromodulation has been used with a reported success rate varying between 47% and 90% in adults with either constipation or fecal incontinence, with only minor adverse events including electrode migration and infection. These encouraging results were conformed in one pediatric study with adolescents with refractory functional constipation not responding to intensive conservative therapy. These promising results with relatively minor adverse events, such as pain after implantation and displacement of the leads, stress the importance of further studies to broaden the role of neuromodulation and to unravel the underlying mechanism of sacral neuromodulation.

Follow-up
The general belief that functional constipation is self-limiting is not supported by several long-term follow-up studies. A systematic review found that only approximately half of all children with constipation followed for 6 - 12 months were doing well, off laxatives. The percentage of children who were free from complaints, regardless of laxative use, after 6 - 12 months was 60.6%. Among these, children treated by subspecialists showed a higher recovery rate than children seen by general pediatricians. No data are available reporting the long-term prognosis of children with constipation treated in primary care. A large cohort of children with constipation who were followed for more than 10 years showed that good clinical outcomes, despite intensive treatment strategies, were achieved only by 80% of patients at 16 years of age. It is therefore necessary to carefully designed randomized trials and to uncover new and more effective interventions for children with constipation.
REFERENCES


OUTLINE OF THIS THESIS

The majority of children with constipation respond well to conservative treatment, including dietary interventions, behavioral therapy and laxatives. A subgroup is not responsive to conventional therapy and continues having complaints of constipation beyond puberty. These patients are a difficult and challenging group for health care professionals and require further investigation. This thesis sheds new light on the pathophysiology of severe childhood constipation, the use of different diagnostic tests and potential novel therapeutic options.

Part I – Epidemiology

Constipation is a common worldwide problem and should be considered a major public health issue in the pediatric population. Knowledge of its epidemiology and influences on quality of life is highly relevant to health care providers. Chapter 1 is a systematic review on the worldwide-published literature to identify the prevalence of constipation in the general pediatric and adult population in order to summarize its geographic, gender and age distribution, and associated socioeconomic factors.

Part II - Pathophysiology

The pathophysiology of constipation in children is multi-factorial and remains incompletely understood. Understanding the underlying mechanisms of defecation disorders in children is crucial for the development of better treatment strategies. Children with defecation disorders often report loss of urge to defecate. To date, a clear explanation for this lack of sensation has never been identified. Previous studies have shown that the role of an increased rectal compliance is limited, but the role of the brain in chronic constipation has yet to be established. Therefore, we propose that cerebral control is impaired, with altered or diminished brain processing of rectal urge sensation. Functional magnetic resonance imaging (fMRI) is a technique to measure changes in regional cerebral activity during stimulation, and has been used in studies to unravel the brain processing of visceral sensation in adults with functional gastrointestinal disorders using. To date, fMRI in combination with rectal distension has never been performed in the pediatric population. In chapter 2 we compare the brain processing of rectal sensation in patients with intractable constipation and healthy controls. Rectal sensation was provoked with a pressure-controlled distension protocol by using a rectal barostat.

Part III - Diagnostics

There are several methods to evaluate gastrointestinal motility and measure colon transit time. Accurate assessment of colonic motility and transit can be essential in the diagnostic work-up, because patients with abnormal colonic function may require different treatment strategies. Colonic scintigraphy is one of the techniques to assess colonic transit. It involves measuring the movement of a capsule containing an isotope (111In of 99Tc), on
gamma-camera images. The clinical usefulness of colonic scintigraphy has to be explored in children and is still considered a research tool in pediatrics. Colonic manometry is a diagnostic test that enables measurement of colonic motor activity. The test is performed in a few specialized motility centers, mostly situated in the United States, to differentiate between normal colonic motor function and colonic neuromuscular disorders on a segmental level. This test is used in clinical practice to identify children who may benefit from surgery. In chapter 3 we compared the diagnostic yield and tolerability of colonic manometry and colonic scintigraphy in children with severe constipation.

Defecography is a dynamic radiologic test performed during voluntary evacuation of the rectum, to assess the anorectal function at rest and during defecation. Although defecography may increase our understanding of the pelvic floor pathophysiology, literature in pediatric patients is lacking and fluoroscopic defecography has not yet proven its value in the management of children with defecation disorders. In chapter 4 we investigated the role of fluoroscopic defecography in understanding the pathophysiology of defecation disorders in children and to describe its value in directing diagnostic and therapeutic management.

**Part IV - Treatment**

Approximately one-third of children with functional constipation is unresponsive to conventional treatment, regardless multiple available medications. Several long-term follow-up studies have shown that good clinical outcomes, despite intensive treatment strategies, were achieved only by 80% of patients at 16 years of age. It is therefore necessary to design randomized trials and to uncover new and more effective interventions for children with constipation. Prucalopride (RESOLOR®) is a selective, high-affinity 5-HT4 receptor agonist, with enterokinetic properties. Several placebo-controlled trials in adults, have demonstrated that prucalopride is effective in increasing stool frequency, reducing constipation-related symptoms and improving quality of life. Chapter 5 contains a phase 3, multi-center, placebo-controlled trial, to determine the efficacy, safety, and tolerability and pharmacokinetics of prucalopride compared to placebo for the treatment of functional constipation in a pediatric population.

A small group of patients has severe, refractory symptoms, unresponsive to intensive medical management. This particular minority may benefit from surgical interventions. The use of antegrade continence enema (ACE) has been reported as a successful therapeutic option for patients with long-lasting constipation when maximal conventional therapy is not successful. Placement of a cecostomy enables delivery of antegrade enemas to evacuate the colon at regular intervals, avoiding accumulation of feces and reducing fecal incontinence. In chapter 6 we describe our 10-year experience with the administration of antegrade enemas in children.