Unraveling childhood constipation: Pathophysiology, diagnostics and treatment
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Summary, discussion, future perspectives

Samenvatting, discussie, toekomst perspectieven
Constipation represents a common worldwide problem in children. In > 90% of children presenting with constipation, no obvious organic cause is found and a diagnosis of functional constipation (FC) is made. Most common symptoms of FC include infrequent bowel movements, painful and hard stools, fecal incontinence and withholding behavior. Children with FC report impaired health-related quality of life in relation to physical complaints and long duration of symptoms. The underlying pathophysiology of childhood constipation is multi-factorial, remains poorly understood, which makes treatment of these patients challenging. Patients with severe, refractory constipation are often referred to specialized centers for further diagnostic testing. Therapy options are limited and are largely based on experience rather than evidence. Therefore, the focus of this thesis is to unravel the pathophysiology, to improve diagnostic strategies and to discover new treatment options for childhood constipation.

Part I - Pathophysiology

Chapter 1 contains a systematic review of the published literature regarding the prevalence of constipation in the general pediatric population. This review shows that the worldwide prevalence rate of pediatric functional constipation varied between 0.7% and 29.6%, with a median of 12%. Female gender, increasing age, socioeconomic status and educational level seemed to affect the constipation prevalence. The wide range in prevalence may be due to the different methods of data collection and the variety of definitions used for FC in the different studies. To date, the Rome III criteria are the most commonly used criteria to define pediatric functional gastrointestinal disorders. These criteria are currently under revision and will be renewed, based on new insights in the literature, into the Rome IV criteria and will be available in 2015. Hopefully these new criteria will be used in future projects to better study the prevalence of constipation. Several genetic and environmental factors have been suggested in chapter 1 to affect the development of constipation. Currently, there is a clear lack of data regarding the prevalence of constipation in developing countries, in particular African countries, and need to be studied further. New studies are currently conducted to elucidate factors associated with pediatric FC, including behavioral problems (e.g. ADHD) and living in war-effected areas.

Part II - Pathophysiology

The pathophysiology of constipation in children is multi-factorial and remains incompletely understood. The most common etiology of functional constipation is withholding of stools, frequently starting after an experience of a hard, painful, or frightening bowel movement. This leads to a vicious circle of stool retention in which the rectum is increasingly distended, resulting in overflow fecal incontinence and loss of rectal sensation. Children with severe chronic constipation often report loss of sensation of urge to defecate, which can’t be explained by previous studies. In chapter 2 we hypothesize that the loss of rectal sensation is related to impaired brain processing of rectal stimulation. Brain-imaging data are, however, lacking in both adults and children with constipation. Therefore we
investigated the cerebral activity in response to rectal distension in children with FC and in healthy controls. The results show that patients with and healthy controls differed substantially with respect to patterns of cerebral activation and deactivation during rectal distension. The differences in BOLD response were observed in multiple brain regions implicated in attentional functions as well as cognition, motor coordination, memory, emotional and sensory association. These results suggest a different neural processing of rectal urge sensation in brain regions previously implicated in adult studies using visceral pain stimuli. The results of this study may support a dysfunction in brain processing of rectal sensation in constipation children rather than leading to direct therapeutic changes in children with FC. However, uncovering and explaining the underlying pathophysiologic mechanism may help patients and their parents to understand the cause of their symptoms and to reassure the families and motivates them to continue with the current often invasive and long-lasting treatment.

Part III - Diagnostics
A minority of patients has, despite intensive therapy, persisting symptoms and need further diagnostic testing. Colonic manometry provides information about colonic motor function on a segmental level; however, the availability of colonic manometry studies is limited to a few pediatric referral centers. Therefore, would it be helpful to identify who would likely benefit from manometry. Colonic scintigraphy involves the measurement of the location of an ingested radioisotope as it transits through the gastrointestinal tract and is more widely available compared to manometry. In adults, colonic manometry and colonic scintigraphy are both valuable studies in discriminating normal and abnormal colonic motility. In chapter 3 we compared the diagnostic yield and tolerability of colonic manometry and colonic scintigraphy in children with severe constipation. Colonic manometry and colonic scintigraphy had a fair agreement regarding the categorization of constipation. Scintigraphy was well tolerated in pediatric patients and in the majority it was preferred over manometry. The results of chapter 3 suggest that scintigraphy can be used as a screening tool for patients with constipation to determine which patients require additional manometry testing. Scintigraphy offers potential advantages (e.g., more accessible, no need for anesthesia) over colonic manometry in children, but larger-scale studies are needed to explore the use of scintigraphy in children. Points of interest should include developing normal pediatric values, possible sex and age difference, the reproducibility and the cost-effectiveness of scintigraphy.

Fluoroscopic defecography can be performed to evaluate anorectal and pelvic floor function in children with severe defecation disorders not responding to medical treatment. Prior studies in adult patients are inconclusive regarding the value of fluoroscopic defecography in clinical decision-making. In chapter 4 we describe that results of defecography in children can be categorized in 3 groups: 1) normal study, 2) pelvic floor dyssynergia and 3) structural anatomical abnormalities. The defecography findings in our study population led to a successful change in clinical management in the majority of patients. To compare results and improve diagnostic reproducibility in future research,
it is important to develop normal pediatric values for defecography measurement and to standardize definitions and techniques. Drawbacks of defecography are that need for cooperation of the patient, which can be difficult in young, frightened children and the radiation exposure of the patient during the study. In recent years, MR defecography has been proposed as an alternative technique to provide insight into pelvic floor and rectal function. However, MR defecography and especially open MR devices that allow sitting position, is still limited in availability.

A broad set of diagnostic tools is currently available for childhood constipation, but their diagnostic utility in the work up of children with severe symptoms remains unclear. Besides MR defecography, several other new diagnostic tools are becoming available, including high-resolution colonic manometry and the wireless motility capsule. Future studies should explore their clinical usefulness in children with defecation disorders.

**Part IV - Treatment**

The treatment of children with chronic constipation can be challenging and may lead to disappointing results for children, parents and health care professionals. Thus, it is crucial to investigate and be familiar with treatment modalities that go beyond traditional and standard care. A potential new drug for treatment of constipation is prucalopride. Prucalopride is a selective, high-affinity, 5-HT4 receptor agonist, with gastrointestinal prokinetic properties. Chapter 5 contains a multicenter, randomized, placebo-controlled, double-blind phase 3 trial to evaluate the efficacy and safety of prucalopride in children with functional constipation aged ≥ 6 months to < 18 years. The results showed that, in contrast with adult data, prucalopride was not more effective than placebo in children with FC. Although prucalopride was generally well tolerated and safe, no significant difference was found in the proportion of responders between treatment with prucalopride (17.0%) or placebo (17.8%). These results implicate that although a drug seems promising in adults, large randomized controlled trials are necessary to be able to make an accurate recommendation in children. The difference in success might be due to a different underlying pathophysiological mechanism present in children compared with adults, most likely withholding behavior. Prior studies have also shown that there is a significant placebo effect of treatment in children. Meanwhile, placebo-controlled trials in children are often questioned, due to ethical considerations. Although, this study demonstrates how important it is to compare new agents to placebo. There remains a need for development of effective and well-tolerated drugs given the fact that a subgroup of children fails to achieve successful clinical outcome with the current available treatment options. Multi-center cooperation remains essential in future studies to retrieve a sufficient patient sample size. Upcoming research on lubiprostone, another potential new laxative drug that has been effective in adults with constipation, will hopefully be successful in children with constipation as well.

A small group of patients is unresponsive to intensive medical management and this particular minority may benefit from surgical interventions. The antegrade continence enema (ACE) has been reported as a possible therapeutic option for defecation disorders
when maximal conventional therapy is not successful. It involves a surgical procedure that enables antegrade delivery of an enema through a cecostomy to clean out the colon at regular intervals, avoiding accumulation of feces and reducing fecal incontinence episodes. In Chapter 6 we describe our 10-year experience with the administration of ACE in children. Results confirm that antegrade enemas are a viable therapeutic option in children with severe constipation, as symptoms of infrequent, painful defecation and fecal incontinence episodes improved with the use of ACE. A sub-group of patients were weaned from the daily use of ACE without recurrence of symptoms. The reason why patients continue being symptom-free after discontinuing the use of ACE cannot be elucidated by our study, but might be the result of resolution or improvement of colon dilatation, attributable to keeping the colon constantly devoid of stools. Other possible explanations could be related to resolution of child’s behavioral problems after experiencing easy, pain-free defecations for several months, ability to recognize the urge to defecate more easily after elimination of chronic stool stasis in the rectum, or maturation of the enteric nervous system over time. Although increasing use of ACE worldwide, there is no consensus regarding the recommended frequency of ACE, the type of irrigation fluid and the addition of a stimulant laxative to the irrigation fluid. Future research is necessary to develop a uniform protocol for the use of ACE in children.

In summary, this thesis provides new insights in pathophysiologic mechanisms that are responsible for chronic constipation; new insights in current available diagnostic tools and new treatment options for childhood constipation. Future studies are needed to further elucidate these issues.