Defecation disorders and chronic abdominal pain in children. Pathophysiology and treatment
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The aim of this thesis was to elucidate possible pathophysiological mechanisms underlying functional defecation disorders and functional abdominal pain in children. In addition, therapeutic modalities based on these pathophysiological mechanisms were evaluated in the different patient groups. The obtained findings contribute to the understanding of these mechanisms and relevant therapeutic strategy and are summarized per chapter.

Chapter 1

The first chapter gives a general introduction into the pediatric functional gastrointestinal disorders; constipation, functional non-retentive fecal soiling and chronic abdominal pain. The anatomy and physiology of rectal function, epidemiology, clinical presentation, pathophysiology, treatment modalities and prognosis of these disorders are discussed.

Chapter 2

The outline of the thesis is described against the background of what is known about pediatric functional gastrointestinal disorders as described in chapter 1. Lacunas in the current knowledge are identified and form the basis for the studies in this thesis.

Chapter 3

Approximately 50% of constipated children contract rather than relax the external sphincter complex during a defecation attempt. Although biofeedback training (BF) is able to change this abnormal defecation behavior, previous studies showed that there is no additional effect on clinical outcome of BF to conventional treatment (CT) compared with CT alone. However, it has been postulated that the absence of a significant difference between these 2 treatment options might be the result of a therapeutic, "demystifying" effect of performing anorectal manometry in the conventionally treated children, which was necessary to obtain basal manometric data. The objective of the prospective, controlled, randomized study described in chapter 3, was to evaluate the effect of CT with 2 anorectal manometry sessions compared to CT alone (which includes dietary advice, diary, toilet training, oral laxatives, and enemas) on clinical outcome. A total of 212 constipated children (143 boys) who were visiting a referral pediatric gastroenterologic practice were prospectively randomized to CT alone (115 patients) or to CT combined with 2 manometry sessions (CTM; 97 patients). Patients were included in the study when they fulfilled at least 2 of the 4 following criteria: stool frequency fewer than 3 per week, 2 or more soiling and/or encopresis episodes per week, periodic passage of very large amounts of stool every 7 to 30 days, or a palpable rectal or abdominal fecal mass. CT consisted of dietary advice, a daily diary, toilet training, and oral laxative treatment preceded by rectal disimpaction with enemas on 3 consecutive days. During both manometries, the child and the parent could watch the tracing on the computer screen. Although the whole procedure was extensively explained to the child, no explanation on the exact meaning of the pressure recordings was given to either the child or the parents during the procedure. When the procedure was finished, the tracings were clarified. Successful treatment was defined as a defecation
frequency of 3 or more per week and fewer than 1 soiling/encopresis episode per 2 weeks and no use of laxatives. Soiling and encopresis was very common in the investigated patients. Only 4 and 2 children from the CT and CTM groups respectively showed no soiling and/or encopresis, whereas 76% and 65%, respectively, reported the periodic passage of large stools. In 26% of the CT and 30% of the CTM patients, a rectal scybalus was found on physical examination. The success rates at 6, 26, 52, and 104 weeks follow-up were 4%, 24%, 32%, and 43% and 7%, 22%, 30%, and 35% in the CT and CTM group, respectively. No significant difference in success percentage was observed between the 2 groups at any time of follow-up with relative risks (CT/CTM) and 95% confidence intervals, respectively, of 0.55 (0.16-1.89), 1.13 (0.67-1.89), 1.07 (0.69-1.65), and 1.23 (0.81-1.85). A significant increase in defecation frequency was observed between the first (intake) and second visit, which was sustained at all subsequent visits and stages of follow up in both groups (not significant). Also in relation to the first visit, a significant decrease in encopresis episodes was found and a further slow but significant decrease at 52 weeks of follow-up in both groups. The initial manometric data obtained from the CTM group showed a low percentage of children with normal defecation dynamics, namely 28%, which (significantly) increased to 38% at the last manometry. Anorectal manometry combined with CT compared with CT alone did not result in higher success rates in chronically constipated children. In conclusion, anorectal manometry has no additional demystifying or educational effect on clinical outcome in chronically constipated children. This observation together with the observations in previous studies which showed no correlation between achievement of normal defecation dynamics and success, and no relation between volume of urge or critical volume and success, leaves no therapeutic role for anorectal manometry in chronically constipated children. The only diagnostic role is restricted to its use as a diagnostic test to exclude Hirschsprung's disease. A simple CT is successful in 30% of severely constipated children who are referred to a tertiary hospital, underscoring the importance of long-lasting and adequate supportive laxative treatment.

Chapter 4

The treatment of children with functional non-retentive fecal soiling, having only complaints of encopresis without any other symptom of constipation, is difficult. They are often treated with regimens used for constipated children, using oral laxatives. This study was initiated to determine whether the combination of laxative treatment and biofeedback therapy (BF) is more effective for the management of children with functional non-retentive fecal soiling than biofeedback therapy alone. In a prospective non-blinded study, 48 children were randomized in 2 groups: treatment with oral laxatives and five sessions of BF (BF + LAX) or five sessions of BF alone (BF) during a treatment intervention period of 7 weeks. Biofeedback was performed with perfused manometry catheters and rectal balloon distension. Training focused on awareness of balloon distension and on instructions to obtain correct defecation dynamics. Successful treatment was defined as <1 encopresis episode per 2 weeks. At the end of the intervention period, the number of encopresis episodes was significantly decreased in both groups: from 7 (range, 2 - 24) to 2 (range, 0 - 17) in the BF group and from 7 (range, 3 - 25) to 2 (range, 0 - 14) in the BF + LAX group. However, significant more children given BF alone fulfilled the predefined criteria for success (less than 1 encopresis episode per 2 weeks) than children treated
with BF and additional oral laxatives (44% vs. 11%). Therefore, there is no additional effect of laxative treatment in children with functional non-retentive fecal soiling. Children treated with BF in combination with laxatives showed a significantly lower success percentage compared with those treated with BF alone. These results suggest that children with functional non-retentive fecal soiling should be treated differently from children with constipation and encopresis. Further research considering these patients as a different entity apart from constipated children is needed both in therapeutic as well as in a pathophysiologic perspective. The first step in developing an adequate treatment regimen for children with functional non-retentive fecal soiling is to come to recognize that these children are clearly different from constipated children. The next step is the sub-classification of this mixed group of children on pathophysiologic or clinical grounds in order to develop a rational therapy. However, due to the very complex anorectal function, combined with an extensive functioning gut-brain axis, in a developing child, it will probably be very difficult to classify all these children. Therefore, a more practical, complementary, therapeutic approach might be of use, in which the use of a new therapeutic modality might sort out subgroups of patients who are successfully treated by that treatment, e.g. gastrointestinal motility influencing regimens, such as loperamide suppositories.

Chapter 5

The possible role of the functional aspects of the rectum in the pathogenesis of childhood constipation and functional non-retentive fecal soiling (FS) is poorly understood. Therefore, a study was designed to evaluate rectal sensation and motility in such patients. Children with chronic constipation (n = 14) and children with FS (n = 14) were studied and compared with healthy volunteers (n = 9). Rectal sensation, compliance and contractility were determined using an intermittent distention procedure using a barostat. The rectal contractile response to a meal was measured after ingestion of a 500 Kcal meal. The main outcome measurements were rectal sensation, rectal compliance, and rectal motility. In constipated children a subgroup (n = 6) showed disturbed rectal compliance, but normal rectal sensation, whereas another subgroup (n = 4) showed decreased rectal sensation for urge, but normal rectal compliance. In a subgroup of children with functional non-retentive fecal soiling (n = 3), rectal sensation for urge was decreased, whereas rectal compliance was normal in all children with functional non-retentive fecal soiling. The rectal contractile response to a meal was comparable between healthy volunteers, constipated children and children with functional non-retentive fecal soiling. In childhood constipation, impaired rectal sensation and increased rectal compliance are major abnormalities that are not related to each other. In contrast to earlier believes, we found disturbed rectal sensation in a minority of children with functional non-retentive fecal soiling, illustrating abnormal rectal function as a possible pathophysiological mechanism in this disorder. These findings underline the need for further research in somatic pathophysiologic mechanisms in children with functional non-retentive fecal soiling and constipation. Furthermore, unraveling these underlying mechanisms might lead to new therapeutic strategies.
Chapter 6

Encopresis in the absence of signs of fecal retention was recently classified as functional non-retentive fecal soiling. The treatment of these children (toilet training in combination with a rewarding system, biofeedback training or behavioural therapy) is often disappointing since only 29% of the patients with functional non-retentive faecal soiling is cured after 2 years of intensive treatment. In the treatment of idiopathic fecal incontinence in adults, which resembles functional non-retentive fecal soiling in childhood, the oral application of loperamide, an opioid agonist, is currently investigated. It has been shown that loperamide lowers rectal contractions and increases anal sphincter tone. Loperamide showed its clinical benefit in adults with idiopathic faecal incontinence. It is unknown if these adults had these complaints of faecal incontinence since childhood. In this chapter, a 20 year old adolescent with functional non-retentive faecal soiling since childhood was treated with loperamide. Loperamide was administered rectally, in the hope, that it will have its effect locally, in a dose of 5 mg twice daily. Since the start of this treatment, the encopresis disappeared. No side effects (abdominal discomfort, nausea and vomiting) were reported. Discontinuation of the medication immediately resulted in a relapse of encopresis. These observations lead to the start of a new study aimed to unravel recto-anal coordination in such children, combined with a prospective placebo-controlled trial evaluating the potential benefit of rectal application of loperamide in the treatment of children with functional non-retentive faecal soiling.

Chapter 7

Children with chronic abdominal pain often present with heterogeneous clinical signs and symptoms, while no organic cause can be identified in most of them. Some children present with symptoms of irritable bowel syndrome. We hypothesized that visceral hypersensitivity and motor abnormalities may be the underlying mechanisms in these children. Rectal sensation and rectal contractile response to a meal were studied in 8 children with IBS and 8 children with functional abdominal pain and those were compared with 9 healthy volunteers. The threshold for pain, but not for first sensation and urge to defecate, was significantly decreased in patients with irritable bowel syndrome (6 ± 1 mm Hg) compared with patients with functional abdominal pain and healthy volunteers (17 ± 1 and 22 ± 2 mm Hg, respectively). In healthy volunteers and patients with functional abdominal pain, ingestion of a meal induced a decrease in rectal volume with an early and late component. This motor pattern was absent in children with irritable bowel syndrome. In patients with irritable bowel syndrome, no rapid volume waves were observed during fasting in contrast to patients with functional abdominal pain (2.7 ± 0.3 / 10 min) and healthy volunteers (1.8 ± 0.5 / 10 min). Children fulfilling the Rome II criteria for irritable bowel syndrome have a significantly lowered threshold for pain and a disturbed contractile response to a meal. Comparable to results reported in adults, sensory and motor abnormalities might play a pathophysiologic role in childhood irritable bowel syndrome. Showing differences in rectal function in children with chronic abdominal pain is important to sub-classify these children in the perspective of possible future treatment strategies. However, at this time it is to early to
speculate on the possible treatment protocols. The recent reviews on treatment possibilities in adults with irritable bowel syndrome are not primarily an exhibition of clear current knowledge in this field, but an illustration of the struggle to understand the treatment options of this disease.

Chapter 8

There are sparse data about the prognosis of childhood constipation and its persistence into adulthood. Therefore, we initiated a prospective follow-up study of children with chronic constipation. From 1993 until 1999, 418 constipated patients older than 5 years at intake (279 boys; mean age 8.4 years) participated in several studies evaluating therapeutic modalities for constipation. All children were subsequently enrolled in the long-term follow-up study, with prospective data collection, after an initial 6-week intensive treatment protocol, at 6 months and thereafter annually, using a standardized questionnaire. Follow up was obtained in more than 95% of the children. The median duration of follow-up period was 5 years (range, 1-8). The cumulative percentage of children who were successfully treated during follow up was 60% at 1 year, increasing to 80% at 8 years. Interestingly, successful treatment was more frequent in children without encopresis and in children with an age of onset older than 4 years. In the group of successfully treated children approximately 50% remained symptom-free during the follow up period, while the other half experienced at least one period of relapse. Relapses occur more frequently in boys than in girls (RR 1.73, 95%CI 1.16 to 2.58). In the subset of children of 16 years and older, constipation was still present in circa 30%. In conclusion, after an intensive initial medical and behavioral treatment, more than half of all children referred to a tertiary medical center for chronic constipation were successfully treated at one year of follow up. One third of the patients continued to have severe complaints of constipation beyond puberty. This finding contradicts the general belief that childhood constipation gradually disappears before or during puberty. Even after successful treatment, intensive follow-up is essential in the treatment of children with constipation.

In conclusion, pathophysiologial mechanisms in childhood functional gastro-intestinal disorders are complex and only partly understood. Consequently, it is difficult to define rational treatment strategies in children with these common disorders. Further studies on pathophysiologic mechanisms might distinguish different subgroups of patients within these groups of children with constipation, functional non-retentive fecal soiling and chronic abdominal pain. The most important message of this thesis is that research in these pediatric patients with functional gastrointestinal disorders has to be continued, since they do not just grow out of it!