Childhood constipation treatment, long-term prognosis and quality of life
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General introduction and Outline of the thesis

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GENERAL INTRODUCTION

Childhood constipation and fecal incontinence

Historical background
Throughout history, bowel irregularity is perceived as dangerous. In the Egyptian pharmaceutical papyrus of the 16th century BC disease is explained by the notion of poisoning of the body by material released from decomposing waste in the intestines \(^1\). For more than three millennia this concept was adopted. In the 19th century it was still propagated that “daily evacuation of the bowels is of utmost importance to the maintenance of health”; without daily movement, “the entire system will become deranged and corrupted” \(^2\). Paradoxically, the germ theory by Pasteur in the last quarter of the 19th century was connected to the concept of internal putrefaction. It was demonstrated that intestinal bacteria broke down protein residues in feces into several components that showed pronounced toxicity when injected to animals \(^3\). The idea that these components in the bowel would somehow spread out into the rest of the body with a general toxic effect, was formulated as the theory of intestinal autointoxication. It was declared that the constipated person in particular “is always working toward his own destruction; he makes a continual attempt at suicide by intoxication” \(^4\). Changes in diet, exercise levels, and pace of life associated with urbanization in industrialized societies was thought to result in an increase of constipation \(^3\). In response, the market for laxatives flourished in the early 1900s. Manufacturers aimed their extensive marketing of laxatives especially on children, trying to convince parents that it was their duty to give laxatives to their children to prevent autointoxication \(^3\). This stopped in the 1930s with growing governmental regulation of advertising as well as the medical profession’s discarding the autointoxication theory. Nonetheless, people in general still associate regular bowel movements with physical health and even nowadays propagation of food supplements (e.g. pre- and probiotics) for a regular bowel pattern continues. Also in medical profession, new theories regarding the association between bowel content and diseases are still developing. Currently, in sharp contrast to the former autointoxication theory, infusions of donated human feces is applied as successful treatment for enteric infections, like Clostridium difficile and ulcerative colitis \(^5, 6\).

The history of fecal incontinence seems to be related to fundamental changes towards human excretory functions during the process of western civilization between 1550 and 1950 \(^7\). During this period, a shift occurred from an open-minded attitude towards (public) urination and defecation into the
situation that these acts were only indirectly mentioned and placed under a taboo. At the end of the 19th century, it became gradually customary in all layers of the western society to wear underclothing both by children and adults. By that time, the increase in publications on fecal incontinence reflects the fact that it was more and more regarded as pathological if children or adults soiled their underwear. Fecal incontinence was either associated with psychological stress and vegetative dysfunctions or related to constipation, but also viewed as a primary psychiatric disorder. In the 20th century the debate on whether fecal incontinence was a physical or psychiatric disorder continued, but currently it is recognized as one of the functional gastrointestinal disorders in children.

**Definition**

To date, the diagnosis functional constipation in infants and children is based on a complex of symptoms in the absence of an underlying organic cause. For many years lack of uniformity on the definition of functional constipation hampered accurate insight in epidemiology and treatment outcome. In the past decades several trials used the Iowa criteria to define childhood constipation, however other less clear definitions were also applied in clinical studies. In order to reach more consensus on the definition of functional gastrointestinal disorders, the Rome criteria have been developed. These criteria distinguish between functional and organic constipation. The Rome III criteria for pediatric functional defecation disorders are as follows:

**Table 1. Rome III criteria for pediatric functional defecation disorders**

**Functional constipation**

Must include two or more of the following:

1. Defecation frequency ≤2 times per week
2. Fecal incontinence ≥1 times per week (after the acquisition of toileting skills)
3. History of retentive posturing or excessive volitional stool retention
4. History of painful or hard bowel movements
5. Presence of a large mass in the rectum
6. History of large-diameter stools that may obstruct the toilet

Accompanying symptoms may include irritability, decrease appetite and/or early satiety. These symptoms disappear immediately following passage of a large stool.

**Functional non-retentive fecal incontinence**

Must include all of the following, in a child with a developmental age of at least 4 years, for at least two months:

1. Defecation into places inappropriate to the social context ≥1 times per month
2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject’s symptoms
3. No evidence of fecal retention.

* Symptoms need to be present at least one month in infants up to 4 years of age is, while for children of 4 years or older a minimum period of two months is stated.
disorders in children, the first pediatric Rome II criteria were formulated in 1999 by a group of experts in the field of pediatric gastroenterology. Subsequently, defecation disorders were divided in Functional Constipation, Functional Fecal Retention and Functional Non-retentive Fecal Soiling. In clinical practice, however the applicability of these criteria were found too restrictive and thus insufficient to identify and assess severity of constipation and monitor treatment outcome. The Rome II criteria for functional constipation or functional fecal retention did not include fecal incontinence, despite the fact that this symptom is the key feature in up to 80% of constipated children. It was further argued that in order to differentiate between retentive and non-retentive fecal soiling, it is necessary to perform a digital rectal examination to assess whether or not fecal impaction is present. Based on these latter studies, the criteria for pediatric functional gastrointestinal disorders were redefined in the Rome III criteria in 2006. Compared to the ROME II criteria, the more neutral term fecal incontinence was adopted instead of the terms encopresis and soiling. Pediatric fecal incontinence is divided in either organic fecal incontinence (e.g. resulting from anorectal malformations or neurologic damage) or functional fecal incontinence. Functional fecal incontinence can be subdivided in constipated-associated fecal incontinence and non-retentive fecal incontinence. The Rome III criteria for functional constipation and functional non-retentive fecal incontinence are given in table 1.

Epidemiology

A recent systematic review reported that the worldwide prevalence of childhood constipation in the general population ranges from 0.7% to 29.6% (median 8.9; inter quartile range 5.3-17.4). Most studies report similar prevalence rates for boys and girls. In a Dutch nationwide study on morbidity in children visiting the general practitioner, the incidence for constipation was found to decrease with age. In infants between 0-1 years of age the incidence was 40/1000 per year, in 2-year olds 22/1000 per year and after the age of 11 the incidence was below 5/1000 per year. Overall, general practitioners saw more girls than boys with constipation. In line with epidemiologic studies in children, varying prevalence rates of functional constipation in adults are reported ranging from 4.6% to 30.9%, largely depending on definitions used. Generally, constipation is reported almost twice as often in women than in men. Epidemiologic studies on the prevalence of fecal incontinence are scarce and generally outdated. In 1966, Bellman reported that the prevalence of fecal incontinence among children over 4 years of age was 1.3%. Prevalence among 7-8 year olds was 2.3% for boys and 1.3% for girls and among 10-12
year olds 1.3% and 0.3%, respectively. A recent population-based study reported an overall prevalence of fecal incontinence of 3.0%\(^{28}\). The presence of fecal incontinence was more frequently found among 5-6 year olds than 11-12 year olds (4.1% versus 1.6%) and found more often in boys than girls (3.7% versus 2.4%). No distinction between functional constipation and non-retentive fecal incontinence was made in these epidemiological studies. In comparison, reported overall prevalence of fecal incontinence in adults varies from 2.7% to 7.4% with increasing prevalence with age but no sex difference\(^{22,29}\).

**Bowel pattern in healthy infants and children**

Stool frequency depends strongly on age in children. In the first month after birth, infants have an average of three stools per day, while between one to twelve months of age this frequency is decreased to twice daily. From the age of three years average stool frequency is once a day, similar to the frequency in adults\(^{30,31}\). It is known that the bowel pattern in infants in the first months after birth is influenced by type of feeding. Breast-fed infants are reported to have a higher defecation frequency and softer stools\(^{31-33}\). Differences in composition between breast- and formula feedings may explain this finding. In recent years, the composition of infant formulas has undergone several changes in order to mimic the effects of human milk. The concept of adding modified triacylglycerol and a mixture of prebiotics, e.g. the nondigestible galacto- and fructo-oligosaccharides, to infant formulas has arisen\(^{34-37}\). Triacylglycerol is a dietary fat consisting of three fatty acids bound to a glycerol molecule. In human milk, the fatty acid palmitic acid is preferentially esterified at the second stereo-specific numbering (sn-2) position on the glycerol backbone, contrary to predominant binding to the sn-1 and sn-3 positions in vegetable (and cows’ milk) fats in infants formulas\(^{34,38,39}\). It has been shown that an infant formula containing high proportion of palmitic acid at the sn-2 position, a mixture of prebiotics and partially hydrolyzed whey protein resulted in softer stools in healthy term infants\(^{40}\). To date, no randomized trials have been conducted to assess the effect of this recently developed infant formula on stool pattern in constipated infants.

Defecation is the complex interplay between muscles of the pelvic floor, the autonomic and somatic nervous system and the group of muscles controlling the anal sphincters. Many children achieve voluntary bowel control around 18 months, but the age at which complete control is attained is very variable. Around the age of 3 years, 98% of the children are toilet trained\(^{41}\). Girls appear to be toilet trained earlier than boys, due to a more rapid maturation, as also expressed by an earlier ability to control bladder function. Development
of bowel and bladder control is a maturational process, which cannot be accelerated by early onset and high intensity of potty-training \(^{42}\). The child’s initiative proves to be a reliable indicator that the child is developmentally capable of being clean and dry. Furthermore, bowel and bladder control is not affected by prematurity, adverse perinatal events or mild to moderate cerebral palsy, nor is it related to psychomotor development \(^{43}\). A marked delay in becoming clean and dry was found in children with severe mental retardation, who are also at a higher risk of developing constipation due to immobility and malnutrition \(^{44, 45}\).

Pathophysiology

The onset of childhood constipation is usually in the first 4 years of life. In approximately 17-40% of constipated children, symptoms already start in their first year of life \(^{33, 46, 47}\). Several organic causes may be underlying: congenital defects of the gut (e.g. Hirschsprung’s disease, anorectal malformations), neurologic diseases (e.g. cerebral palsy, spinal cord disorders) and endocrine, renal or metabolic disorders (e.g. hypothyroidism, renal tubular acidosis, cystic fibrosis). Yet an organic cause is found in only 5-10% of children, while in all other cases the disorder is functional in origin.

In toddlers, withholding behavior plays an important role in the development and/or persistence of functional constipation. The time of toilet training is thought to be a critical period when constipation may occur as a consequence of struggle between child and parents \(^{48}\). Interestingly, Borowitz et al. found no association between timing, style or techniques used for toilet training and development of early childhood constipation \(^{49}\). On the other hand, a study by Burket et al. found that constipated children, especially between 2-3 years of age, were perceived by their parents as more stubborn, both in general and specifically regarding toileting behavior than children without constipation \(^{50}\). This stubbornness could play a role in development of constipation or influence treatment response at a younger age \(^{50}\). Several other reasons may also lead to stool withholding behavior in children: 1) previous experience with painful or hard stools, 2) anal fissures, 3) lack of time for regular toileting, 4) resistance to use toilets other than the child’s own, 5) stressful events, and 6) intercurrent illness \(^{49, 51}\). Retained stools become progressively more painful and difficult to evacuate leading to even more fear and avoidance of defecation \(^{14, 52}\). As a result of withholding behavior, retained stools cause increasing distention of the rectum \(^{13}\). Chronic distention of the rectum subsequently leads to overflow incontinence, a frustrating symptom for both child and parents. Long-term fecal impaction may eventually result in a dilated rectum with
decreased rectal tone and decreased rectal contractility contributing to delayed evacuation of feces. Finally, impaired rectal function rather than withholding stools might lead to persisting of infrequent defecation. Normal rectal sensation, but higher distensability (compliance) of the rectum was found in constipated children compared to healthy children. This finding suggests that the rectum is stretched and larger stool volumes are needed to trigger rectal sensation, such as the urge to defecate. A recent study however showed that increased rectal compliance was still found in almost half of the recovered adolescents, indicating a limited role of disturbed rectal compliance in therapy resistant functional constipation. The role of increased rectal compliance in the pathophysiology of intractable constipation still needs to be elucidated with prospective studies.

The underlying mechanism of functional non-retentive fecal incontinence (FNRFI) is largely unknown. In scientific literature, controversial ideas about etiology have been postulated focusing either on disturbed gastrointestinal motility and sensation or on presence of psychological disturbance and psychiatric morbidity. Pathophysiology seems to be complex and FNRFI is most likely a multi-factorial disorder.

Fecal continence depends on a variety of dynamic responses to movement of feces, such as colonic contractions, rectal compliance and accommodation and internal and external anal sphincter responses. In addition, mechanoreceptors in the rectal wall, the afferent nerve pathway and cerebral processing play a role in both conscious perception and homeostatic, visceromotor, or reflexive functions. Abnormal dynamics at one or more levels may be involved in the pathophysiology of fecal incontinence.

Colonic transit times within the normal range confirmed frequent bowel movements in children with FNRFI. Furthermore, no significant impairment of anorectal sensorimotor function in these children was found. However, 50% of children with FNRFI presented with abnormal defecation dynamics, e.g. inability to relax the external anal sphincter during defecation. Nonetheless, normalization of defecation dynamics through biofeedback training did not result in higher success rates. Contraction of the external anal sphincter during defecation may be an acquired control mechanism of the child in order to unconsciously retain the rest of stools in the rectum after loss of first stool in underwear.

In contrast to the volume-controlled distention with anorectal manometry, rectal balloon distention by barostat using a pressure-controlled distention protocol provides a more refined assessment of sensation and compliance. Rectal barostat testing showed that, in contrast to constipated children, patients with FNRFI have normal rectal sensation and compliance. These
findings further underlined the clinical and manometric findings that indicated that FNRFI is a distinct clinical entity from constipation. In some patients with FNRFI undergoing a barostat, rectal contractions accompanied by unnoticed fecal loss were observed. These rectal contractions were not followed by an increase in anal sphincter pressure as adequate to prevent fecal loss. In adults with idiopathic fecal incontinence, similar observations were measured by anorectal manometry. Furthermore, in children with fecal incontinence caused by anorectal malformations or sacral neurologic defects, there is evidence of aberrant huge amplitudes of rectal contractions, described as an "automatic" rectum. This description shows resemblance with the symptoms of a substantial part of the children with FNRFI, who indicate that they only notice feces at the time it reaches their underwear, sometimes shortly after an acute irresistible urge. Further research is necessary to explore whether FNRFI may result from a disruption in interactions of rectal contractions and compensation reflex of the anal sphincter complex. Neglecting anorectal sensation as a result of altered cerebral processing may also play a role.

Historically, psychiatrists have viewed fecal incontinence in children as an emotional disturbance, representing an impulsive action triggered by unconscious anger. Several studies associated fecal incontinence with different behavioral traits, such as moodiness, disobedience, attention deficits, hyperactivity, poorer social competence and learning disabilities. Cox et al. showed that children with fecal incontinence have more anxiety/depression symptoms, family environments with less expressiveness and poorer organization, more disruptive behavior and poorer school performance compared to children without fecal incontinence. It was stated that high prevalence of behavioral symptoms might represent primary emotional problems in these children resulting in fecal incontinence.

Pediatricians have argued that behavioral problems, if present, are generally secondary to social consequences and humiliation experienced by these children due to the presence of fecal incontinence. Gabel et al. found mild behavioral problems in 49% of children with fecal incontinence, but these behavioral scores indicated less severe behavioral problems than usually found in children referred to mental health services. Friman's study showed similar behavioral scores in both children with and without fecal incontinence. A study by Van der Plas et al. reported significantly more behavioral problems, mostly internalizing problems, in a subgroup of 35% of children with FNRFI. Successful treatment led to a significant improvement of behavioral profile in these children. These results supported the idea that occurrence and maintenance of behavioral problems in children with FNRFI is secondary to presence of fecal incontinence. Benninga et al. found no differences in the
behavior profiles between children able or unable to relax their pelvic floor muscles during defecation attempts. Similar findings were earlier observed in children with fecal incontinence as result of constipation. In a recent cross-sectional study, children with fecal incontinence showed significant higher rates of emotional and behavioral problems compared to children without fecal incontinence. Frequent incontinence was associated with more difficulties, such as oppositional behavior and involvement in overt bullying (as both perpetrator and victim), compared to occasional incontinence. No comparison between retentive and non-retentive fecal incontinence could be made as no clinical assessment for constipation was done.

To date, the question whether behavior problems result in defecation disorders or vice versa is a major point of issue and yet difficult to answer. In our experience only in a minority of these children, e.g. those who exhibit social withdrawal, low self-esteem and depressive behavior, or in case of treatment resistance and family problems, referral to a mental health professional is needed. The role of fecal incontinence therefore has to be interpreted as the important factor in the occurrence and maintenance of the behavioral problems in children with defecation disorders.

**Diagnostic work-up**

The cornerstones for diagnosis of FC and FNRFI are a careful medical history and complete physical examination including a rectal digital examination. The medical history should include questions about the child’s bowel pattern from birth up to the present moment. Information about the passage of meconium, age of onset of bowel problems, defecation frequency, stool consistency and size, occurrence of rectal blood loss, pain during defecation, passage of large amount of stools and retentive posturing is of major importance. Fecal incontinence frequency, with details of time (daytime and/or nighttime) and situation (during playing outside, behind TV/computer) of occurrence, needs to be elicited. Accompanying symptoms such as abdominal pain, poor appetite and urinary incontinence should be assessed. A dietary (both qualitative and quantitative) history on food and fluid intake and the previously applied treatment strategies should also be determined. General information about growth, use of medication and neuromuscular development need to be obtained. Information on psychological or behavioral problems and family life events (such as birth of siblings, divorce of parents and decease of a family member) is essential. Finally, one should always be aware of warning signs that suggest the possibility of sexual abuse.
Complete physical and neurological examination should be performed in all children with defecation disorders. Abdominal examination gives valuable information concerning accumulation of gas or feces. Perianal inspection provides information about position of the anus, perianal feces, redness, dermatitis, eczema, fissures, hemorrhoids and scars. It is important to consider the possibility of sexual abuse if upon examination anal fissures and scars are found without evidence of a medical cause for these abnormalities. These anal findings are reported to be significantly more present in children with a history for anal sexual abuse. Anorectal digital examination assesses perianal sensation, anal tone, size of rectum, amount and consistency of stool in rectum, voluntary contraction and relaxation of anal sphincter and the presence of an anal wink.

In general pediatric practice, a plain abdominal radiograph is frequently used to objectify fecal loading in children with signs of constipation and/or fecal incontinence. However, conflicting data exist concerning the value of a plain abdominal radiograph in diagnosing constipation. A recent systematic review assessed the evidence from controlled studies concerning the association between scoring fecal loading on a abdominal radiograph and clinical signs and symptoms in children. Based on these studies, it was concluded that a radiographic diagnosis of constipation occurs almost as often in clinically constipated as in clinically non-constipated children. Therefore a plain abdominal radiograph has no value in the diagnostic work-up of children with functional defecation disorders.

Additional use of radio-opaque markers in order to assess colonic transit time (CTT) is thought to obtain more valuable information about colorectal motor function than a plain abdominal radiograph. With the Bouchoucha method patients ingest daily a capsule containing 10 markers during 6 consecutive days and on day 7 a single radiograph is obtained to calculate transit time. With this technique both overall colonic transit and segmental transit can be determined to distinguish different transit patterns: 1) normal colonic transit time: normal transit through all colonic segments; 2) outlet obstruction: delayed transit through the anorectal region and 3) slow transit constipation: prolonged transit through the entire colon. In approximately 50% of constipated children CTT is delayed. In the majority of these children the delay of transit is found in the anorectal region. Symptom severity in these patients was assessed with a bowel diary for daily self-report of the child’s defecation pattern, including defecation and fecal incontinence frequency, consistence and size of stool, painful defecation, abdominal pain and enuresis. More severe symptoms of constipation are found to correlate strongly with prolonged CTT. Moreover, self-reported symptoms in a bowel
diary have shown to correspond with the actual bowel habit of the child. Thus, emphasizing that an adequate inventory of clinical symptoms makes assessment of CTT superfluous. On the contrary, the marker test has proven useful in differentiating between children with constipation and children with FNRFI. Ninety percent of children with FNRFI have normal CTT. In children with fecal incontinence, a normal CTT in combination with a normal defecation pattern without a fecal mass on physical examination confirms the diagnosis FNRFI. This underlines again the importance of a thorough clinical history and physical examination to diagnose functional constipation and FNRFI.

If neurological abnormalities are present on physical examination, an underlying closed spinal dysraphism, such as intradural lipoma, filar lipoma, dermal sinus and thigh filum terminale, needs to be excluded. Alarming neurological signs include motor and sensory dysfunction of the lower extremities and abnormal reflexes, or abnormal anorectal sensation and anal wink. In children presenting with these abnormalities a MRI of the spinal cord is required. A recent study revealed spinal cord abnormalities with MRI in 9% of children with intractable constipation. After surgical repair, constipation resolved in 86% of these children. This was a retrospective study of severely constipated patients not responding to aggressive clean-out regiments, which of course limits interpretation of these results. Prospective studies are needed to further evaluate the prevalence and clinical relevance of spinal cord abnormalities in constipated children.

Several techniques can be used to assess anorectal function. Anorectal manometry measures through volume-controlled distention pressures in the anorectal region and is useful to assess sphincter function and contraction patterns. Barostat measurements, using pressure-controlled distention, give valuable information about rectal sensitivity and contractility. At this moment, there is no indication for routinely performing anorectal manometry or barostat in children with constipation and fecal incontinence, as findings have no clinical implications. Therefore these techniques will not be discussed in detail here.

Treatment

The backbone for treatment of FC consists of education of the child and parents, behavioral modifications and laxative therapy. Education on the physiology of defecation and demystification of the pathogenesis of constipation are important first steps in treatment. In general, concerns about defecation frequency must be set off against normal variability in defecation patterns within a population. In approximately 80% of constipated children fecal
incontinence is a main clinical feature, often frustrating both child and parents \textsuperscript{17}. The physician must explain that constipation and fecal incontinence are common problems in children, so that families feel less isolated. Furthermore, negative and guilty feelings need to be discussed. It is important to explain that fecal incontinence is often involuntary and happens as result of overflow incontinence due to fecal impaction. The parents should be explained that the child may not always be aware of fecal accidents. The child is used to the odor of feces surrounding him and therefore not smelling this unpleasant scent. When other people intrude his territory they instantly smell the odor of feces. For parents and other care givers it is often unthinkable that the child does not feel the need to go to the toilet or bathroom to change clothes. By addressing these issues, a positive and non-accusatory approach needs to be encouraged at all times during treatment. It should also be emphasized that treatment is often long-lasting and relapses after initial success are common.

Implementation of behavioral recommendations, such as toilet training and a reward system aims to restore normal bowel habits. Training consists of trying to defecate for 5 minutes after each meal and immediately after school time, since this is the time of day most of these children experience their fecal incontinence. In addition, the child and parents keep a daily bowel diary to gain better insight in the defecation and fecal incontinence frequency and time of occurrence. During treatment the diary illustrates improvement. Again, a non-accusatory gentle approach is needed and therefore a rewarding system is useful. A previous study found that successful outcome in constipated children was higher in those receiving a combination of behavioral interventions and laxative therapy than those treated with behavioral interventions alone \textsuperscript{96}. On the other hand, there is some evidence that behavioral interventions added to laxative therapy has advantage over laxative therapy alone for improving continence in children with constipation-associated fecal incontinence \textsuperscript{97-99}.

Indistinct descriptions of medical and/or behavioral interventions across studies hamper comparison of current findings \textsuperscript{98, 99}. Many studies may report on medical treatment and behavior interventions, but lack clear distinction between behavior recommendations made by physicians and behavior therapy implemented by pediatric psychologists. To overcome this problem, pediatric psychologists recently developed a protocolized behavior intervention program for constipated children \textsuperscript{100}. This program based on cognitive-behavioral theories was derived from a multidisciplinary behavioral treatment already used for children with defecation disorders \textsuperscript{101}. The efficacy of this behavioral intervention needs to be evaluated by well-designed randomized controlled trials.
Laxative therapy has a two-fold role in treatment of constipation: 1) disimpaction and 2) maintenance. If fecal impaction is present upon abdominal and/or rectal examination, disimpaction is necessary before initiation of maintenance therapy. Disimpaction by rectal route, e.g. rectal enemas or stimulant suppositories, or oral route, using polyethylene glycol, or a combination of the two have shown to be effective 102-105. Once disimpaction is accomplished, maintenance therapy is essential to prevent re-accumulation of feces. Daily oral laxative therapy needs to be continued for 3 months or longer at a dose that produces a daily soft stool without side effects. Compliance to oral laxatives needs to be controlled frequently. An extensive overview of different oral laxatives is given elsewhere 83, 95. A subgroup of children may be unresponsive to treatment with oral laxatives. These children experience recurrent fecal impactions, clinically characterized by long intervals between defecation episodes, passage of large amount of stools once every 7-30 days and fecal incontinence. Recurrent fecal impaction in these children may be related to higher compliance of the rectum found in constipated children 54. It is hypothesized that application of rectal enemas on a regular basis in addition to oral laxatives might prevent repeated fecal impactions and subsequently positively influence rectal compliance and/or rectal function.

Derived from the treatment approach for constipated children, children with FNRFI are conventionally treated with education, behavioral modifications (toilet training and rewarding system) and keeping a bowel dairy 106. Laxatives are contra-indicated in these children, as they already have a normal defecation frequency 64. Other medical treatment options such as loperamide have been suggested, but its efficacy for treatment of FNRFI needs to be further studied 66. There is no evidence that biofeedback training adds any benefit to conventional treatment in the management of FNRFI in children 63. No data exist on the role of psychological therapy for FNRFI. In future, well designed randomized controlled trials to determine other treatment options of FNRFI are needed 63.

Follow-up

Several studies have assessed long-term follow-up of constipated children. Staiano et al. followed 62 children for a period of 5 years 107. In half of the constipated children symptoms persisted during this follow-up period, meaning that they still experienced less than 4 bowel movements per week. Interestingly, fecal incontinence frequency decreased significantly irrespective of constipation outcome. Another study with a median follow-up period of 4 years found that 66% of 137 constipated children were cured, although no
clear definition of constipation was given. In this study, fecal incontinence at time of presentation was not associated with worse outcome at follow-up. A third follow-up study by Van Ginkel et al. assessed follow-up in 403 constipated children. Success was defined as defecation frequency of 3 or more times per week with less than 2 episodes of fecal incontinence for a period of 4 weeks. Cumulative percentage of successfully treated children during total follow-up time of 8 years was 80%, while 60% was already achieved at 1 year follow-up. At least one relapse occurred in 50% of the children within the first 5 years after initial treatment success. Persistence of symptoms of constipation into young adulthood was present in one third of all patients. But it needs to be noted here that only 12% of the followed children had reached the age of 18 years at last follow-up. In contrast to the previously mentioned study, successful outcome was higher in children without fecal incontinence at time of presentation.

Recently, a small study explored the relationship between functional childhood constipation and functional gastrointestinal disorders, such as constipation and irritable bowel syndrome, in adulthood. A history of childhood constipation appeared to be a predictor of IBS in adulthood. This study followed only 20 patients into adulthood, so prospective follow-up studies with larger samples should further investigate outcome of childhood constipation. Follow-up of constipated children is important as relapse after successful treatment and persistence of symptoms into adulthood are not uncommon.

To our knowledge only one study described long-term follow-up in children with FNRFI. Hundred-fourteen children with FNRFI were followed for approximately 10 years and clinical success was defined as having less that 1 episode of fecal incontinence in 2 weeks while not using medication, such as loperamide, for at least one month. After 2 years of intensive medical and behavioral treatment, only 29% of children were successfully treated. Thereafter a steady increase in success percentage was seen: 65% and 90% at 5-years and 10-years follow-up, respectively. Successful treatment according to biological age showed that at the age of 12 years still 49% of patients with FNRFI were not successfully treated. At 18 years of age, 85% of patients were free of symptoms. The fact that FNRFI persisted in 15% of children is in contrast with the assumption that fecal incontinence is unusual after 16 years of age. No prognostic factors for success were found. This follow-up study is limited by a bias in the study population. Only patients with such severe symptoms that referral to a tertiary medical center was necessary were included. Follow-up studies in primary health centers are needed to provide further information on the prognosis of FNRFI.
Health-related quality of life

This section discusses the definition of quality of life in relation to health, the methods how to apply this concept in children and its interaction with course of life. Furthermore, an introduction is outlined on the implications for measurement of health-related quality of life (HRQoL) and course of life in constipated children and young adults.

In the past decades it has become more important to measure efficacy of treatments and evaluate morbidity for diseases in term of Health-related quality of life (HRQoL) $^{112}$. The concept of HRQoL has developed as a separate outcome measure next to the traditional outcomes, such as biochemical or physiological parameters. In 1948, the World Health Organization (WHO) defined health as "a state of complete physical, mental and social well being and not merely the absence of disease or infirmity" $^{113}$. Derived from this definition, many definitions of QoL exists, but all agree on three key ideas: 1) individuals have their own unique perspective on QoL; 2) QoL is conceptualized as a multidimensional construct encompassing several domains, including at least four 'core' domains: physical, cognitive, social and emotional functioning; and 3) QoL can include both objective and subjective perspectives in each domain $^{112, 114, 115}$. Against this background, HRQoL refers to QoL in which a dimension of personal judgment over one’s health and disease is added $^{116}$.

In the pediatric setting, advances in medical care have resulted in improved outcome of many diseases, but subsequently caused a raise in chronic conditions in children $^{117}$. To date, an estimated 10-20% of all children during childhood and adolescence are affected by chronic diseases $^{118, 119}$. With this shift from mortality to morbidity, the need for assessment of HRQoL in children increased. Children may be affected by disturbed physical and psychosocial function as a result of the disease or treatment $^{120, 121}$. Difficulties in measuring children’s HRQoL are the quality of measures, the question of age-sensitivity and proxy rating $^{122}$. With age and developmental level the meaning of HRQoL changes, thus sensitive measures are needed for different age groups. This may complicate assessment of HRQoL over time in individuals. Furthermore, for children younger than 8 years or children with cognitive problems, measurement of HRQoL depends on parent-proxy ratings. Several studies found inconsistency between child self-report and parent-proxy report, indicating that parent proxy is not a straightforward substitution of the child’s rating of HRQoL $^{114, 123-125}$. Combined measurement of child self-report and proxy rating is therefore preferable.

Two categories of instruments can be used to measure HRQoL: generic instruments, assessing the range of domains of QoL and applicable to
different patient populations, and disease specific questionnaires, assessing concerns that may be particular to a disease, function, or population\textsuperscript{112}. Generic questionnaires have the advantage that comparison between different patient populations and available normative data from healthy populations is possible. On the other hand, measurement with generic questionnaires may lack sensitivity to disease specific factors that have an impact on HRQoL. Disease specific questionnaires are therefore more sensitive to determine HRQoL within specific patient groups. Ideally both types of questionnaires are used to assess HRQoL.

Growing up with chronic disease may impede a child’s development. Full-filling of age-specific developmental tasks in childhood is of great importance to the adjustment in adult life\textsuperscript{126}. Normal developmental tasks of childhood and adolescence involve attainment of social and academic competence, development of peer relationships and increasing independence from the parents\textsuperscript{127}. The term ‘Course of life’ refers to these necessary developmental tasks and resulting developmental milestones. A Dutch course of life questionnaire to assess the achievement of developmental milestones retrospectively was recently developed by the psychosocial department of the Emma Children’s hospital/Academic Medical Center\textsuperscript{128}. Hampered or delayed achievement of developmental tasks may influence the child’s HRQoL.

Chronic symptoms of functional constipation in children are associated with a lower quality of life, as measured with generic questionnaires\textsuperscript{129}. Children themselves reported lower quality of life, mainly due to impaired physical ability. Parents reported even lower quality of life than their children, which was probable impacted by the duration of their child’s symptoms and by family members having similar symptoms\textsuperscript{129}. Not only in constipated children, but in all children with functional defecation disorders, as defined by the ROME II criteria, lower quality of life is found compared to healthy controls\textsuperscript{130}. Whether specific disease characteristics, such as presence of fecal incontinence, explain this lower HRQoL, is better measured with a disease specific instrument.

Recently, such a disease specific questionnaire, the Defecation Disorder List (DDL), has been developed to measure self-reported HRQoL in children with constipation and fecal incontinence\textsuperscript{131}. Several phases of development (e.g. item generation, item reduction/phrasing/formatting, pilot testing of the questionnaire, last modifications of the pre-final instrument and reliability/validity testing) were followed using accepted guidelines\textsuperscript{132}. In a small group of 27 patients good reliability and test-retest stability was found, making the DDL a promising tool for measurement of disease specific HRQoL. Further testing in a larger patient cohort is still needed to confirm previous findings.
Follow-up studies showed that in the majority of children with constipation, with or without fecal incontinence, long-term prognosis is favorable. On the other hand, the general belief that children with constipation “just grow out of it” with the onset of puberty has been refuted. Symptoms may even persist beyond 18 years of age. Chronic constipation may cause significant interference with normal childhood physical and emotional maturation. Feelings of shame and frustration and negative parent-child interaction caused by constipated-related fecal incontinence may have a negative impact on the psychosocial and social development in children. One could hypothesize that especially in adolescents, constipation and fecal incontinence can negatively influence peer interaction and psycho-sexual development. To date, no data exists on the HRQoL or the accomplishment of developmental tasks in those patients with persisting of chronic constipation and fecal incontinence at an adult age. Comparison of these patients with healthy peers might gain insight in the impact of these disorders on children. Recognition of impaired QoL and course of life in these patients is important, as it may provide targets for additional (non-medical) intervention in an earlier phase of treatment.

In summary, functional constipation and fecal incontinence in children are worldwide recognized as common problems. Treatment of these functional disorders is challenging, as symptoms often persist for years and relapses are frequent. Despite extensive studies of the colon and anorectal parameters in the past decades, there is still a lack of insight in underlying pathophysiological mechanisms. Subsequently, current treatment strategies are mainly symptomatic, and remain unsuccessful in a subgroup of patients. Better insight in pathophysiology and determinants of prognosis may improve treatment outcome. Overall in children with functional constipation and fecal incontinence, persistence of these symptoms into adulthood occurs in 30% and 15%, respectively. Whether these chronic symptoms have an impact on the health-related quality of life and social development of these patients needs to be further elucidated.
OUTLINE OF THE THESIS

The studies in this thesis discuss potential novel therapeutic options for children affected by functional constipation at different ages. Furthermore, it aims to improve insight in long-term outcome and health-related quality of life in children and young adults with chronic childhood constipation. **Part I – Clinical interventions for functional constipation** focuses on three new treatment strategies for childhood constipation in infants and school aged children with chronic constipation. **Part II – Prognosis of functional constipation** describes long-term outcome of childhood constipation and evidence-based prognostic factors. **Part III – Health-related quality of life and chronic constipation** discusses quality of life related to childhood constipation in two different contexts. 1) measurement of disease specific health-related quality in constipated children and 2) measurement of generic health-related quality of life and accomplishment of developmental tasks in young adults with therapy resistant constipation.

Part I – Clinical interventions for functional constipation

Changes to infant formula in order to mimic human milk were found to positively influence frequency and consistency of stools in healthy term infants. In Chapter 1, we evaluated in a double-blind, randomized cross-over trial the clinical effect of a modified infant formula, comprising triaglycerol and a mixture of oligosaccharides, in term infants with constipation. Stool withholding behavior is thought to play a key role in development and/or persistence of functional constipation in children. The vicious circle of painful defe¬cation, stool withholding and passage of large, hard stools can be described as learned behavior. Recently, a specifically developed behavioral therapy focusing on this learned behavior and conducted by pediatric psychologists may influence stool withholding behavior thereby improving treatment outcome in constipated children. Chapter 2 describes a randomized controlled trial comparing the efficacy of this behavioral therapy to conventional therapy, consisting of a combination of toilet training and laxatives, in constipated children. After years of intensive conventional treatment, 30-40% of constipated children are found to be refractory to treatment. Many of these children experience recurrent episodes of fecal impaction, clinically presenting with long intervals between defecation episodes, passage of large amounts of stools and fecal incontinence due to overflow. We hypothesized that maintenance treatment with regular application of rectal enemas in addition to oral laxatives
may result in higher success rates and prevent frequent relapses in constipated children unresponsive to oral laxative treatment. A randomized trial comparing these two regimens is reported in Chapter 3.

Part II – Prognosis of functional constipation
In Chapter 4 the currently available literature regarding the prognosis of functional constipation in children and factors that influence prognosis is discussed in a systematic review.
Scarcely data exists on the outcome of childhood constipation in patients reaching adult age. The general thought that children “just grow out of it” is further examined by extension of the prospective follow-up of a previously described Dutch cohort of constipated children 109. This study describes the long-term outcome and investigated prognostic factors for successful outcome (Chapter 5).

Part III – Health-related quality of life and chronic constipation
Functional constipation is a chronic disorder in a small subgroup of children. In the past decades, health-related quality of life (HRQoL) is developed as an independent outcome measure to gain insight in the impact of a chronic disorder on affected children. Recently, a disease specific HRQoL questionnaire was developed for children with constipation and fecal incontinence 131. The applicability of this questionnaire was further tested in a cohort of children with chronic constipation (Chapter 6).
A study, in which HRQoL in young adults with persisting symptoms of childhood constipation was compared to successfully treated young adults and healthy peers is described in Chapter 7. Subsequently, in these patient groups the course of life was determined to analyze whether specific milestones of normal childhood development were reached despite suffering of chronic constipation (Chapter 8).

This thesis closes with a summary and discussion of the results of the preceding chapters.
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General introduction and Outline of the thesis

