Childhood constipation treatment, long-term prognosis and quality of life
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Thesis, University of Amsterdam, The Netherlands


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Childhood Constipation
Treatment, Long-term Prognosis and Quality of Life

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Faculteit der Geneeskunde
“Write on my tablets all that was permitted,
All that was for our human senses fitted.
Then the events of this wide world I’d seize
Like a strong giant, and my spirit teaze
Till at its shoulders it should proudly see
Wings to find out an immortality.”

John Keats (from: Sleep and Poetry)
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*Ammale Nestlé (Engl)* 2007; 65:81-88

*Journal of Pediatric Gastroenterology and Nutrition* 2007;44(1):5-13
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. 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”. 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. 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”. Changes in diet, exercise levels, and pace of life associated with urbanization in industrialized societies was thought to result in an increase of constipation. 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. 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. 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. 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 8 or related to constipation 9, but also viewed as a primary psychiatric disorder 10-12. 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 13, 14.

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 14. 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 15, however other less clear definitions were also applied in clinical studies. In order to reach more consensus on the definition of functional gastrointestinal

<table>
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<th>Table 1. Rome III criteria for pediatric functional defecation disorders 14, 19</th>
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| **Functional constipation**<sup>+</sup> 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 voluntary stool retention  
4. History of painful or hard bowel movements  
5. Presence of a large mass in the rectum  
5. 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 included 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\textsuperscript{26, 27}. A recent population-based study reported an overall prevalence of fecal incontinence of 3.0%\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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. 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. 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.

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. 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. Interestingly, Borowitz et al. found no association between timing, style or techniques used for toilet training and development of early childhood constipation. 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. This stubbornness could play a role in development of constipation or influence treatment response at a younger age. 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. Retained stools become progressively more painful and difficult to evacuate leading to even more fear and avoidance of defecation.

As a result of withholding behavior, retained stools cause increasing distention of the rectum. 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 FNFRI 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, greater social problems, 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 defeation 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 thight 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 defeation and demystification of the pathogenesis of constipation are important first steps in treatment. In general, concerns about defeation frequency must be set off against normal variability in defeation patterns within a population. In approximately 80% of constipated children fecal
incontinence is a main clinical feature, often frustrating both child and parents. 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. 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. Indistinct descriptions of medical and/or behavioral interventions across studies hamper comparison of current findings. 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. This program based on cognitive-behavioral theories was derived from a multidisciplinary behavioral treatment already used for children with defecation disorders. 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
A clear definition of constipation was given\(^{108}\). 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\(^{109}\). 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\(^{108}\), successful outcome was higher in children without fecal incontinence at time of presentation\(^{109}\).

Recently, a small study explored the relationship between functional childhood constipation and functional gastrointestinal disorders, such as constipation and irritable bowel syndrome, in adulthood\(^{110}\). 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\(^{106}\). 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\(^{106}\). 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\(^{106}\). 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\(^{111}\). 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 terms of Health-related quality of life (HRQoL)\textsuperscript{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”\textsuperscript{113}. Derived from this definition, many definitions of QoL exist, 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\textsuperscript{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\textsuperscript{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\textsuperscript{117}. To date, an estimated 10-20% of all children during childhood and adolescence are affected by chronic diseases\textsuperscript{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\textsuperscript{120,121}. Difficulties in measuring children’s HRQoL are the quality of measures, the question of age-sensitivity and proxy rating\textsuperscript{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\textsuperscript{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: \textit{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. 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. Normal developmental tasks of childhood and adolescence involve attainment of social and academic competence, development of peer relationships and increasing independence from the parents. 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. 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. 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. 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. 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. 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. 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 triacylglycerol 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 defecation, 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.

Scarce 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. 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. 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.
REFERENCES

21. Linden MW van der S-SLvSFWJvd. Tweede Nationale Studie naar ziekten en verrich-


94. Nurko S. Gastrointestinal manometry, methodology and indications. In: Walker W,


General introduction and Outline of the thesis


Part I

Clinical interventions for functional constipation
Chapter 1

The clinical effect of a new infant formula in term infants with constipation: a double-blind, randomized cross-over trial

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ABSTRACT

Background
Nutrilon Omneo (new formula; NF) contains high concentration of sn-2 palmitic acid, a mixture of prebiotic oligosaccharides and partially hydrolyzed whey protein. It is hypothesized that NF positively affects stool characteristics in constipated infants.

Methods
Thirty-eight constipated infants, aged 3-20 weeks, were included and randomized to NF (n=20) or a standard formula (SF; n=18) in period 1 and crossed-over after 3 weeks to treatment period 2. Constipation was defined by at least one of the following symptoms: 1) defecation frequency < 3/week; 2) painful defecation; 3) abdominal or rectal palpable mass.

Results
Period 1 was completed by 35 infants. A significant increase in defecation frequency (NF: 3.5 pre versus 5.6/week post treatment; SF 3.6 pre versus 4.9/week post treatment) was found in both groups, but was not significantly different between the two formulas (p= 0.36). Improvement of hard stool consistency to soft stool consistency was found more often with NF than SF, but did not reach statistical significance (90% versus 50%; RR, 1.8; 95% CI, 0.9-3.5; p= 0.14). No difference was found in painful defecation or the presence of an abdominal or rectal mass between the two groups. Twenty-four infants completed period 2. Only stool consistency was significantly different between the two formulas (17% had soft stools on NF and hard stools on SF; no infants had soft stools on SF and hard stools on NF, McNemar test p= 0.046).

Conclusion
The addition of a high concentration sn-2 palmitic acid, prebiotic oligosaccharides and partially hydrolyzed whey protein resulted in a strong tendency of softer stools in constipated infants, but not in a difference in defecation frequency. Formula transition to NF may be considered as treatment in constipated infants with hard stools.
INTRODUCTION

Between 16-40% of the infants with constipation experience symptoms before the age of six months \(^1\)-\(^3\). In approximately 90% of infants no specific organic cause can be found \(^4\). It is well established that the bowel pattern in infants is influenced by the type of feeding in the first months after birth. Constipation is more commonly found in formula-fed infants, who have a greater tendency to produce hard stools compared to breast-fed infants \(^5\). Differences in the composition between breast- and formula feeding may explain this finding.

The structure of lipids differs between human milk and infant formulas. In both human milk and infant formulas palmitic acid is the predominant saturated fatty acid. In human milk 70-85% of palmitic acid is positioned at the sn-2 position of the triacylglycerol molecule, whereas in regular infant formulas 88-94% of palmitic acid is found at the sn-1 and sn-3 position \(^6\)-\(^10\). Lipolysis of triacylglycerol by pancreatic lipase occurs predominantly at the sn-1 and sn-3 positions, yielding free fatty acids and a 2-monooacylglycerol \(^11\), \(^12\). Subsequently, free palmitic acid may form insoluble calcium fatty acid soaps which are excreted via the feces, resulting in firmer stools. Stool hardness has been positively associated with the presence of calcium fatty acid soaps in the stools \(^5\). In human milk however, palmitic acid esterified at the sn-2 position of the triacylglycerol molecule is well absorbed as 2-monopalmitin, since it readily forms mixed micelles with bile acids \(^11\), \(^13\)-\(^15\).

Human milk is further known to be a rich source of oligosaccharides \(^16\). These oligosaccharides resist digestion in the small intestine and thus reach the colon unaltered, where they serve as prebiotics \(^17\). They act as growth substrate for bifidobacteria, which are thought to have beneficial effects on the host’s health by supporting the gut barrier, stimulating normal intestinal function, and strengthening the immune system \(^18\)-\(^20\). In addition, due to their non-digestibility, they may be considered to be a form of soluble fibres and contribute to the softer stools produced by breast-fed infants \(^17\), \(^21\).

Based on these findings, the concept of adding modified triacylglycerol and prebiotic oligosaccharides to infant formulas has arisen. A new infant formula (NF; Nutrilon Omneo, Nutricia Nederland BV, Zoetermeer, the Netherlands) was developed which contains modified vegetable oil with a high proportion (41%) of palmitic acid at the sn-2 position, a mixture of prebiotic oligosaccharides, partially hydrolyzed whey protein and reduced lactose content. The oligosaccharides mixture consists of 90% short-chain galacto-oligosaccharides (GOS) and 10% long-chain fructo-oligosaccharides (lcFOS), 0.8g/100ml, and resembles human milk oligosaccharides with respect to its molecular weight distribution and high galactose content \(^22\). The effect of NF
on stool frequency and consistency has been assessed in one study in healthy term infants. Infants receiving NF were found to produce softer stools than those fed a regular infant formula. We hypothesized that this NF will also have a positive effect stool characteristics in constipated infants.

METHODS

Patients

This study was conducted in the academic medical hospital in Amsterdam and 5 non-academic hospitals in the Netherlands. Eligible for the study were otherwise healthy, term infants with constipation, between 3 - 20 weeks of age, who received at least 2 bottles of milk-based formula per day. Constipation was defined as the presence of at least one of the following symptoms: 1) frequency of defecation < 3/week; 2) painful defecation (crying); 3) abdominal or rectal palpable mass. Children with Hirschsprung’s disease, spinal or anal anomalies, previous colonic surgery, metabolic, cerebral and renal abnormalities were excluded. Also children who were treated with laxatives at enrollment were excluded. The medical ethics committees of the participated hospitals approved the research protocol. All parents gave written informed consent.

Medical history and physical examination

At enrollment, clinical history, dietary history, obstetrical data and anthropometry were recorded. The infants were randomized by a computer program to either NF or SF in period 1 and crossed-over after 3 weeks to treatment period 2. In order to mimic the taste of Nutrilon Omneo, the whey-based control formula was partly mixed with a formula based on hydrolyzed whey protein (mixture of 75% Nutrilon 1 and 25% Aptamil HA). Further details on the composition of the study formulas are given in Table 1. Formula cans were labeled with codes to mask identity of the study feedings. Neither the parent nor the physicians were aware of the composition of the formula until the entire study was completed. During both periods parents were asked to daily record in a diary details on formula intake, formula tolerance (vomiting, flatulence, colics, rash), passage of stools and stool consistency compared to four validated photographs of runny, mushy soft, formed soft and hard stools. After each intervention period, an out-patient clinic visit for evaluation of data was done. During these visits, anthropometric assessments and abdominal and rectal examination were performed.
Efficacy parameters

In this study it was hypothesized that the use of NF would alleviate the symptoms of constipation. The following primary efficacy parameters were assessed: 1) defecation frequency > 3/week; 2) normalization of stool consistency; 3) no more painful defecation; 4) absence of abdominal or rectal palpable mass at physical examination. Secondary outcome measures were formula tolerance and weight gain.

Statistical analysis

Prior to the start of the study, sample size, based on a cross-over design, was calculated to allow detection of a 30% difference in improvement between NF and SF. Under the assumption of a significance level of 0.05 with a power of 0.80, and 2-sided hypothesis testing, a minimal sample size of 34 with 17 children in each group was determined.
Descriptive statistical measures were calculated for baseline characteristics. Our cross-over study was hampered by the drop-out of a substantial number of children after they finished period 1 and before or during the second period of treatment (Figure 1). Only 24 children (63%) completed the cross-over study. It is highly likely that drop-out occurred not at random, but was related to clinical outcome (for instance early termination in period 2 because of insufficient response). A cross-over analysis of the completers within this study could therefore lead to biased results. Therefore we restricted our main analysis to the first period. Essentially, this reduces our trial to a simple, two-group parallel trial, but we rather sacrifice loss-of-power than introducing bias. Comparisons between the two treatment groups after period 1 were performed using ANCOVA in case of continuous outcomes and χ² tests for categorical endpoints. However, we do present the results of the patients that finished the cross-over trial to evaluate whether the results are in the same line as the first period results. The subgroup analysis was performed using either a paired sample t test or the McNemar test for paired observations. Differences were considered statistically significant when the P-value was less than 0.05.

![Figure 1. Trial profile](image)

* No contact after intake. ** In period 1 three patients on SF dropped out; 2 patients stopped because of severe constipation; one patient switched to hypoallergenic feeding, because of suspected cow’s milk protein allergy. *** Parents of 1 patient decided that they did not want to cross-over because she was free of symptoms and they started openly with NF instead. **** Three patients dropped out after switching to NF; 2 patients stopped after less than 1 week because of recurrence of constipation symptoms. 1 patient was lost to follow-up. ***** Seven patients dropped out after switching to SF; 6 patients stopped after one week because of recurrence of constipation symptoms. One patient was lost to follow-up.
RESULTS

Patient characteristics

Between April 2002 and January 2004, 41 constipated infants were enrolled in the study. Directly after inclusion 3 infants dropped out for unknown reasons, because parents did not show up at the next outpatient clinic visit. Thus, 38 patients were randomized and received either SF (n=18) or NF (n=20). Figure 1 shows a scheme of the trial profile. A total of 35 infants completed the first period of 3 weeks. Only 24 patients completed the full cross-over study. The various reasons for withdrawal of the study are described in the legends of Figure 1. Data analysis was based on the group of 35 patients that completed period 1 and a subgroup analysis of 24 patients who completed the cross-over.

The median age at enrollment of the 38 infants (19 male) was 1.7 months, whereas the median age at onset of constipation was 2 weeks. The mean defecation frequency was 3.5/week and 45% of all infants had a defecation frequency of less than 3 times per week. Furthermore, the main symptoms of constipation were hard stool consistency and painful defecation, occurring in 61% and 82% of infants respectively. Baseline characteristics of the infants according to randomization to SF or NF are described in Table 2.

Table 2. Baseline characteristics of infants with functional constipation by randomized group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SF (n=18)</th>
<th>NF (n=20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of boys (%)</td>
<td>11 (61)</td>
<td>8 (40)</td>
<td>0.19</td>
</tr>
<tr>
<td>Age at intake (in months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>1.8</td>
<td>1.7</td>
<td>0.80</td>
</tr>
<tr>
<td>min-max</td>
<td>1.1-5.0</td>
<td>0.7-3.7</td>
<td></td>
</tr>
<tr>
<td>Age of onset (in weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>2.0</td>
<td>2.0</td>
<td>0.45</td>
</tr>
<tr>
<td>min-max</td>
<td>0.20</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Defecation frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/week (mean ± SD)</td>
<td>3.6 ± 1.8</td>
<td>3.5 ± 2.6</td>
<td>0.64</td>
</tr>
<tr>
<td>&lt; 3 times/week</td>
<td>39%</td>
<td>50%</td>
<td>0.49</td>
</tr>
<tr>
<td>Hard stool consistency</td>
<td>72%</td>
<td>50%</td>
<td>0.16</td>
</tr>
<tr>
<td>Painful defecation</td>
<td>89%</td>
<td>75%</td>
<td>0.27</td>
</tr>
<tr>
<td>Abdominal scybalus</td>
<td>44%</td>
<td>20%</td>
<td>0.13</td>
</tr>
<tr>
<td>Rectal scybalus</td>
<td>29%</td>
<td>21%</td>
<td>0.51</td>
</tr>
<tr>
<td>Meconium passage &lt; 48 hours</td>
<td>100%</td>
<td>90%</td>
<td>0.32</td>
</tr>
<tr>
<td>Positive family history</td>
<td>61%</td>
<td>58%</td>
<td>0.84</td>
</tr>
</tbody>
</table>

SF = standard formula; NF = new formula.
Clinical efficacy after period 1

Compared to baseline, a significant increase in mean defecation frequency /week was found after 3 weeks from 3.5/week to 5.3/week (difference between means, 1.8; 95% CI: 0.81 - 2.78; p=0.001). Mean defecation frequency /week increased from 3.5/week pre to 5.6/week post treatment with NF compared to 3.6/week pre to 4.9/week post treatment with SF, but the increase in frequency was not significantly different between the groups (difference between means, 0.7; 95% CI, -0.8 - 2.3; p = 0.36, ANCOVA) (Table 3). Improvement of hard stool consistency at intake to soft stool consistency after 3 weeks intervention was found more often with NF than SF, but did not reach statistical significance (90% versus 50%; RR, 1.8; 95% CI, 0.9 - 3.5; p= 0.14). Furthermore, painful defecation diminished in both groups; NF: 75% pre and 65% post treatment and SF: 89% pre and 67% post treatment. Also a decrease in the presence of an abdominal and/or rectal mass was found; NF: 35% pre and 10% post treatment and SF: 44% pre and 5.6% post treatment. However, no significant differences in both of these patient characteristics were found between the two feeding groups (Table 3).

Table 3. Clinical efficacy of standard formula (SF) versus new formula (NF) after period 1

<table>
<thead>
<tr>
<th></th>
<th>SF (n=15)</th>
<th>NF (n=20)</th>
<th>Difference of means (95% CI)*</th>
<th>RR (95% CI)**</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defecation</td>
<td>4.9 ± 2.5</td>
<td>5.6 ± 2.8</td>
<td>0.7 (-0.8-2.3)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement of</td>
<td>50% (5/10)</td>
<td>90% (9/10)</td>
<td>1.8 (0.9-3.5)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>hard to soft</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stools (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No painful</td>
<td>33% (5/15)</td>
<td>35% (7/20)</td>
<td>1.0 (0.4-2.7)</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>defecation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No abdominal or</td>
<td>93% (14/15)</td>
<td>90% (18/20)</td>
<td>1.0 (0.8-1.2)</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>rectal mass</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* ANCOVA; ** χ² tests

Clinical efficacy after cross-over (period 1 and 2)

Only 24 infants completed the cross-over study. In these infants, the defecation frequency was comparable for NF and SF with a mean frequency of 5.5/week vs. 5.9/week (Difference of means, - 0.5; 95% CI, -1.6 – 0.6; p= 0.38), respectively. The frequency of soft stools was significantly higher in the NF period, with 17% (n=4) of infants having soft stools when receiving NF but hard stools with SF, compared to no infant with soft stools when receiving SF and hard stools with NF (McNemar test, p= 0.046). Painful defecation and the presence of abdominal or rectal mass were not significantly different between the periods on NF and SF.
Safety
Throughout the study there were no serious adverse effects in either group. Both formulas were well tolerated. Weight gain was similar in both feeding groups. In period 1 NF fed-infants gained 29.7 grams/day whereas weight gain in infants fed SF was 32.2 grams/day (difference of means, -2.6; 95% CI, -11.7 - 6.6; p= 0.57). In the subgroup that completed the cross-over phase of the study, growth was not significantly different between the periods on NF and on SF; 28.2 grams/day versus 33.5 grams/day respectively (difference of means, -5.4; 95% CI, -13.0 - 2.3; p= 0.16).

DISCUSSION
To our knowledge this is the first double-blind cross-over study evaluating the effect of Nutrilon Omneo (NF) on stool characteristics in infants with constipation. Our data show that constipated infants with hard stools fed NF, containing a high proportion of sn-2 palmitic acid and a mixture of prebiotic oligosaccharides, improved more often to softer stools compared to whey-based SF-fed infants. Defecation frequency increased significantly compared to baseline in both groups, but was not different between the NF-fed and SF-fed infants. The formula was well tolerated and growth rates were similar on both formulas.

Previous studies in healthy infants revealed a wide variability in defecation frequency depending on age and the type of feeding 21, 24, 25. Fontana et al. showed a decline in defecation frequency from an average of 3 stools per day in the first month of life to 1.4 per day at 3 years of age 24. Furthermore, breast-fed infants have a defecation frequency twice as high as formula-fed infants in the first 12 weeks of life 21. In this study in infants with constipation, the mean defecation frequency at enrollment was 3.5 times per week. A total of 45% of all infants presented with a defecation frequency of < 3 times/week. Two recent follow-up studies in constipated infants found different defecation frequencies at enrollment of 6.5 times per week and 2 times per week, respectively 26, 27. This disparity is most likely explained by the difference in patient populations. The study by Loening-Baucke et al. and our study were conducted in infants referred to general pediatric out-patient clinics. In the study by Van den Berg et al. only infants with severe functional constipation that required referral to a specialized clinic to rule out Hirschsprung’s disease were included. The difference in age distribution between the studies may also have contributed to the difference in outcome, since we included younger infants up to 5 months

New infant formula in term infants with constipation
of age, but the other two studies included children up to a maximum of 2 years of age\textsuperscript{26, 27}.

In comparison to these recent follow-up studies in constipated infants, we found a higher percentage of infants with painful defecation (82%). Hard stool consistency in more than half of the infants just partially explains this finding, since the presence of painful defecation did not improve in accordance with a softer stool consistency. Loening-Baucke et al. reported hard stool consistency in 93% of all constipated children and painful defecation in only 41%. Van de Berg et al. did not report on stool consistency, but painful defecation was present in 49% of the infants. Differences may be explained by the fact that painful defecation at this young age is a very subjective measurement and difficult to objectify by a parent on a daily basis. The fact that this study was a multi-centre trial may also have lead to an inter-observer difference in the registration of changes in painful defecation.

In our analysis infants receiving NF showed more improvement of hard stools to soft stools than those fed SF, although significance was only reached in infants completing the cross-over study. This result is in line with the findings of two previous studies demonstrating softer stools in healthy term infants fed high \textit{sn}-2 palmitate formula\textsuperscript{9, 15}. This effect is attributed to a reduced fecal excretion of calcium-fatty acid soaps\textsuperscript{5, 28}. Another explanation for the difference in stool consistency is most likely the addition of a prebiotic mixture of GOS/lcFOS in the Nutrilon Omneo formula. Earlier studies in healthy infants have shown that supplementation of an infant formula with this mixture resulted in an increased number of fecal \textit{Bifidobacteria} and softer stool consistency\textsuperscript{23, 29, 30}.

Moro et al. found that this effect was dose-dependent and softer stools were comparable to stools of breast-fed infants at a level of 0.8 g/100ml of GOS/FOS mixture\textsuperscript{30}. Similar to our results, Schmelzle et al. showed softer stools, but no statistical difference in defecation frequency in healthy term infants fed NF\textsuperscript{23}. This positive effect on stool consistency is of clinical importance in our patient population, as a majority of infants (61%) presented with hard stool consistency as main symptom of their constipation.

Additionally, previous studies have shown that formulas containing hydrolyzed protein can produce softer stools\textsuperscript{31}. Therefore, the presence of hydrolyzed whey protein may also have contributed to the stool softening effect of NF. In this respect, the addition of some hydrolyzed protein (about 25% of total protein) to SF may explain the observed increase of defecation frequency on both formulas. However, the observed increase in defecation frequency was stronger in infants fed NF than those fed SF, but no significant difference was found.
A limitation of this study is that more than one third of the constipated infants enrolled did not complete the study protocol. Due to this high drop-out rate, no cross-over data was available from these children resulting in loss of power in our analysis. Therefore our findings on defecation frequency and stool consistency need to be confirmed in a larger clinical trial in order to gain more insight into the effects of the composition of this NF.

This drop-out rate is of further concern because it may potentially introduce a bias. However, besides a significantly lower age at enrollment in the drop-out group, baseline characteristics showed no difference between the infants who dropped out and the remaining infants. There was a relationship between the drop-out rate and the feeding type, since the most important reasons for drop-out were: 1) a significant improvement after the first treatment period on NF, or 2) the recurrence of symptoms of constipation after the switch to SF in the second period. Understandably, parents refused to continue the study when their infant had improved or when symptoms of constipation recurred. In general, parents of sick children have emotional and ethical problems to accept the risk of recurrence of the initial symptoms. The latter is probably the reason for the lack of scientific data evaluating the effect of infant formulas or oral laxatives in infants with constipation.

In conclusion, this study demonstrates that the use of an infant formula with a high proportion of \textit{sn}-2 palmitate, a mixture of prebiotic galactooligosaccharides and fructo-oligosaccharides and partially hydrolyzed whey protein may lead to softer stools in constipated infants. Thus, constipated infants who present with hard stools may benefit from a change from SF to this NF as a first treatment step, but larger randomized clinical trials on the efficacy of this new formula are needed.

\textbf{Acknowledgements}

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REFERENCES


New infant formula in term infants with constipation


Behavioral therapy for childhood constipation: a randomized controlled trial

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ABSTRACT

Objective
It has been suggested that addition of behavioral interventions to laxative therapy improves continence in children with functional fecal incontinence associated with constipation. Our aim was to evaluate the clinical effectiveness of behavioral therapy with laxatives compared to conventional treatment in treating functional constipation in childhood.

Patients and methods
In this randomized controlled trial conducted in a tertiary hospital in the Netherlands 134 children aged 4-18 years with functional constipation were randomly assigned to 22 weeks (12 visits) of either behavioral therapy or conventional treatment. Primary outcomes were defecation frequency, fecal incontinence frequency and success rate. Success was defined as defecation frequency of ≥3 times per week and fecal incontinence frequency of ≤1 times per two weeks irrespectively of laxative use. Secondary outcomes were stool-withholding behavior and behavior problems. Outcomes were evaluated at end of treatment and at 6-months follow-up. All analyses were done by intention to treat.

Results
Defecation frequency was significantly higher for conventional treatment (IRR=0.75, 95%CI=0.59-0.96; p=.021). Fecal incontinence frequency showed no difference between treatments. After 22 weeks, success rates did not differ between conventional treatment and behavioral therapy (respectively 62.3% and 51.5%), nor did it differ at 6-months follow-up (respectively 57.3% and 42.3%). The proportion of children withholding stools was not different between interventions. At follow-up, the proportion of children with behavior problems was significantly smaller for behavioral therapy (11.7% vs. 29.2%; RR=0.42, 95%CI=0.18-0.96; p=.039).

Conclusion
Behavioral therapy with laxatives has no advantage over conventional treatment in treating childhood constipation. However, when behavior problems are present, behavioral therapy or referral to mental health services should be considered.
INTRODUCTION

Constipation in children is a worldwide problem with a prevalence ranging from 0.7% to 29.6% \(^1\). Up to 84% of functional constipated children suffer from fecal incontinence \(^2\) and over one third exhibit behavior problems \(^3, 4\). It remains unclear whether behavior problems are primary or secondary to functional constipation.

In the vast majority of patients no somatic cause can be found and therefore these patients are considered to have a functional defecation disorder \(^5\). Retentive posturing or stool-withholding behavior is probably the major cause for development and/or persistence of childhood constipation \(^6-11\). Retained stools become progressively more difficult and painful to evacuate, leading to fear and avoidance of defecation \(^12, 13\). This vicious cycle can be described as learned behavior.

Based on clinical experience, constipated children are traditionally treated by pediatricians combining laxative treatment with behavioral approaches, like toilet training and education. Long-term follow-up studies showed, however, that despite intensive medical treatment functional constipation persists into young adulthood in one-third of patients \(^14, 15\).

In treating childhood constipation, it seems important to address defecation avoidance and to treat behavior problems. There is some evidence that the adjunct of behavioral interventions to laxative therapy, rather than laxative therapy alone, improves continence in children with functional fecal incontinence associated with constipation \(^16-18\). We developed a protocolized behavioral therapy for constipated children and their parents. The present study aimed to evaluate this behavioral therapy with laxatives compared to conventional treatment. It was hypothesized that behavioral therapy with laxatives would result in more success regarding constipation, stool-withholding behavior, and behavior problems.

METHODS

Patients

The study population consisted of children with functional constipation aged 4-18 years referred by general practitioners, school doctors, and pediatricians to the gastrointestinal outpatient clinic at the Emma Children’s Hospital in Amsterdam, the Netherlands. Inclusion took place between November 2002 and August 2004. At entry patients had to meet at least two of four criteria: defecation frequency <3 times per week, fecal incontinence ≥2 times per week,
passage of large amounts of stool at least once every 7–30 days (large enough to clog the toilet) or a palpable abdominal or rectal fecal mass. Children were excluded if they had received a comprehensive behavioral therapy in the previous 12 months. Children using drugs influencing gastrointestinal function other than laxatives and children with organic causes for defecation disorders such as Hirschsprung’s disease, spina bifida occulta, hypothyroidism or other metabolic or renal abnormalities were also excluded. The medical ethics committee of the Academic Medical Center of Amsterdam approved the study protocol. All patients and/or parents gave written informed consent.

Baseline assessment
One week before baseline assessment the pediatric gastroenterologist asked the parents to consider participation in the study. Parents were assigned to discontinue any laxative treatment and to record in a bowel diary frequency of stools and episodes of fecal incontinence. The criterion of a standard amount of stool was illustrated to parents with a clay model. Fecal incontinence was defined as any amount of feces in the underwear. The next week eligibility was verified and a physical examination, including digital rectal examination, was performed to evaluate presence of an abdominal or rectal fecal mass. Baseline data for primary and secondary outcome measures were obtained. The parent that accompanied the child to the outpatient clinic filled out the questionnaire for the secondary outcomes.

Design
The study had a two parallel group, randomized controlled design. After baseline measurement and if written informed consent was given, a research assistant performed a telephone call to a randomization center and revealed the allocation to parents immediately. A computer-based system was used to generate a sequence of random group assignment for consecutive patients. Randomization was stratified by age (4-8 years or ≥ 8 years) and gender. Within two weeks after randomization, patients received their first treatment session.

Intervention
The intervention period for both conventional treatment (CT) and behavioral therapy (BT) consisted of 12 visits during 22 weeks with similar intervals between treatment sessions. CT and BT employed similar laxative therapy. Disimpaction with daily Klyx® enemas (sodium-dioctylsulfosuccinate and sorbitol; 60 ml/day for children ≤ 6 years of age; 120 ml/day for > 6 years of age) for three
Consecutive days was prescribed by pediatric gastroenterologists before starting treatment. Maintenance therapy consisted of polyethylene glycol 3350 (PEG 3350) one sachet (10 g) per day and if treatment was considered to have insufficient effect the dose was increased by one sachet. If spontaneous defecation was delayed for more than three days, parents were advised to give an enema or bisacodyl suppository of 5 mg. In BT, it was preferred to give oral bisacodyl tablets of 5 mg instead of rectal laxatives. During behavioral therapy pediatric psychologists adjusted laxative dose and consulted a pediatric gastroenterologist when necessary. In both treatment groups patients kept a bowel diary.

Conventional Treatment
CT was conducted by pediatric gastroenterologists and consisted of visits lasting approximately 20-30 minutes during which laxative treatment (PEG 3350 and if necessary Klyx® enemas or bisacodyl suppositories) and the bowel diary were discussed. Patients and their parents received education to explain that symptoms are not harmful and are common in children with functional constipation and that a positive, nonaccusatory approach is essential. Furthermore, children were instructed not to withhold stool when they feel urge to defecate. Motivation was enhanced by praise and small gifts from the pediatric gastroenterologists.

Protocolized Behavioral Therapy
BT was developed by pediatric psychologists of the psychosocial department of our hospital. Basic assumption is that phobic reactions related to defecation can be reduced and that adequate toileting behavior and appropriate defecation straining can be (re)acquired by teaching parents behavioral procedures and by behavioral play therapy with the child in presence of its parents. The protocol consists of two age-related modules: a module for children aged 4-8 years and a module for children aged ≥8 years. The learning process for child and parents consists of five sequential steps: Know, Dare, Can, Will, and Do. This approach is derived from a multidisciplinary behavioral therapy to treat children with defecation disorders. For all involved psychologists a detailed manual for both age-related modules was available to ensure a standard delivery of therapy. Visits lasted approximately 45 minutes.
Clinical Outcomes

Primary outcome measures were: defecation frequency per week, fecal incontinence frequency per week and successful treatment. Treatment was considered successful if patients achieved a defecation frequency of ≥3 times per week and a fecal incontinence frequency of ≤1 times per two weeks irrespectively of laxative use.

Secondary outcome measures were: stool-withholding behavior and, behavior problems. Stool-withholding behavior was scored on a three-point scale (yes, sometimes, no) by asking parents if they observed that their child holds his legs stiffly together or crosses them when feeling urge to defecate. Behavior problems were assessed by the Child Behavior Checklist (CBCL/4–18) \(^{24}\). This questionnaire obtains parent’s report of their child’s behavior problems at the time of administration and for the preceding six months. Behavioral ratings were compared with a normative sample of Dutch children \(^{25}\). The CBCL yield scores for a Total problem scale, and for an Internalizing (withdrawal, somatic complaints and anxiety/depression) and Externalizing (delinquency and aggression) behavior problem scale. A T-score higher than 63 (90\(^{th}\) percentile) is a well-validated cut-off discriminating between non-referred and referred children to mental health centers. It indicates whether a child needs professional help for his problems \(^{24}\).

Assessments in each intervention arm took place at the last visit (posttreatment time point) and six months after the 22 week-treatment was ended (follow-up). Time between baseline assessment and follow-up approximately was one year. Follow-up assessment was carried out by telephone by pediatric gastroenterologists. Assessment of behavior problems at both time points was done by a research assistant who sent parents one Child Behavior Checklist with a stamped addressed envelope to return the questionnaire. Parents decided whether the mother or the father filled out the questionnaire at home.

Sample size

The sample size was calculated to allow detection of a 25% difference in the proportion of success between behavioral therapy and conventional treatment. It was estimated that conventional treatment reached success in 35% of the children at follow-up \(^{26}\). Under the additional assumption of a significance level of .05, a power of .80, and 2-sided hypothesis testing, a minimal sample size of 124 with 62 children in each group was determined.
Statistical analysis

Intent-to-treat analyses were conducted using SAS version 9.1.3 and STATA version 9.2. Due to withdrawal before treatment start, drop-outs during the study, failure to fill out questionnaires, or research procedure violations missing data occurred. Imputation of missing values was used to make intent-to-treat analyses feasible. Missing data were imputed using IVEware (Imputation and Variance Estimation Software), which uses a general-purpose multivariate imputation procedure (sequential regression imputation method) that can handle relatively complex data structures when data are missing. It produces imputed values for each individual in the data set conditional on all the values observed for that individual. In this manner ten different datasets were created. All analyses were performed using these ten datasets and then aggregated by averaging the individual results.

Independent sample t-tests were used to test differences in continuous variables and Chi-square tests when the variables were categorical for the sample description at baseline. The proportion of patients that dropped out before end of treatment was tabulated and compared using Chi-square or Fisher’s Exact tests.

To determine the effect of treatment on defecation frequency and fecal incontinence frequency, negative binomial regression models were fitted with treatment (conventional treatment, behavioral therapy), time (posttreatment, follow-up), and treatment-by-time as factors. To control for possible differences in baseline values, defecation or fecal incontinence frequency at baseline were included in the model as covariates. For these regression models a robust variance estimator was used. For all binary outcome measures, a risk ratio model was applied. The effect of treatment condition on the proportion of successfully treated children, stool-withholding behavior and CBCL behavior problems (T-score > 63) was derived using generalized linear models for the binomial family with treatment, time, and treatment-by-time interaction as factors in the model. Again, baseline measures were included to control for differences in baseline values. For stool-withholding behavior and the three CBCL scales, the proportion of children at baseline was included, while success rate was adjusted for the baseline value of defecation and fecal incontinence frequency. Adjusted means and proportions were derived from the regression models based on their linear predictions. Estimated values (adjusted) rather than observed (unadjusted) values are presented throughout the paper unless otherwise specified. A p-value < 0.05 was considered statistically significant.
RESULTS

Sample

A total of 134 patients were assigned to conventional treatment or behavioral therapy (Fig 1). During treatment 2/64 (3.1%) in the CT group and 9/65 (13.8%) in the BT group discontinued intervention (p=.054). At follow-up four patients

Figure 1. Patient flow chart
dropped out in CT. There was one loss of contact and three children were referred for behavioral therapy directly after conventional treatment, making them unsuitable for follow-up measurements. Questionnaires were not returned by three patients in both intervention arms at posttreatment and by nine patients (CT: 6, BT: 3) at follow-up. Baseline characteristics are presented in Table 1. Except for painful defecation (p=.014), there were no significant differences found between the two groups in sociodemographic factors, nor for clinical characteristics.

Table 1. Baseline characteristics of children allocated to conventional treatment or behavioral therapy

<table>
<thead>
<tr>
<th></th>
<th>Conventional Treatment (n=67)</th>
<th>Behavioral Therapy (n=67)</th>
<th>N</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>6.5 (2.1)</td>
<td>6.9 (2.5)</td>
<td>134</td>
<td>.367</td>
</tr>
<tr>
<td>Boys, N (%)</td>
<td>37 (55.2)</td>
<td>39 (58.2)</td>
<td>134</td>
<td>.727</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of onset constipation, mean (SD), y</td>
<td>3.0 (2.0)</td>
<td>2.8 (1.9)</td>
<td>134</td>
<td>.551</td>
</tr>
<tr>
<td>Period of treatment, mean (SD), mo</td>
<td>17.1 (19.4)</td>
<td>18.7 (21.7)</td>
<td>129†</td>
<td>.673</td>
</tr>
<tr>
<td>Positive family history, N (%)</td>
<td>28 (43.8)</td>
<td>33 (50.8)</td>
<td>131†</td>
<td>.338</td>
</tr>
<tr>
<td><strong>Outcome measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defecation frequency/week, mean (SD)</td>
<td>1.9 (2.7)</td>
<td>2.0 (2.3)</td>
<td>134</td>
<td>.961</td>
</tr>
<tr>
<td>Fecal incontinence/week, mean (SD)</td>
<td>15.6 (15.9)</td>
<td>15.0 (14.2)</td>
<td>134</td>
<td>.831</td>
</tr>
<tr>
<td>Stool-withholding behavior, N (%)</td>
<td>44 (68.8)</td>
<td>43 (67.2)</td>
<td>128†</td>
<td>.850</td>
</tr>
<tr>
<td>CBCL Total score, N (%)*</td>
<td>26 (38.8)</td>
<td>23 (34.3)</td>
<td>133‡</td>
<td>.591</td>
</tr>
<tr>
<td>CBCL Internalizing score, N (%)*</td>
<td>25 (37.3)</td>
<td>23 (34.3)</td>
<td>133‡</td>
<td>.719</td>
</tr>
<tr>
<td>CBCL Externalizing score, N (%)*</td>
<td>18 (26.9)</td>
<td>18 (26.9)</td>
<td>133‡</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Additional clinical symptomatology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painful defecation, N (%)</td>
<td>39 (65.0)</td>
<td>28 (43.1)</td>
<td>125†</td>
<td>.014</td>
</tr>
<tr>
<td>Hard stools, N (%)</td>
<td>19 (32.2)</td>
<td>14 (22.2)</td>
<td>122†</td>
<td>.215</td>
</tr>
<tr>
<td>Large amount of stool, N (%)</td>
<td>46 (68.7)</td>
<td>45 (67.2)</td>
<td>134</td>
<td>.853</td>
</tr>
<tr>
<td>Abdominal pain, N (%)</td>
<td>46 (69.7)</td>
<td>46 (68.7)</td>
<td>133†</td>
<td>.897</td>
</tr>
<tr>
<td>Day time urinary incontinence, N (%)</td>
<td>12 (17.9)</td>
<td>10 (14.9)</td>
<td>134</td>
<td>.641</td>
</tr>
<tr>
<td>Night time urinary incontinence, N (%)</td>
<td>23 (34.3)</td>
<td>19 (28.4)</td>
<td>134</td>
<td>.456</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal scybalus, N (%)</td>
<td>20 (31.3)</td>
<td>22 (35.5)</td>
<td>126§</td>
<td>.614</td>
</tr>
<tr>
<td>Rectal scybalus, N (%)</td>
<td>27 (49.1)</td>
<td>38 (58.5)</td>
<td>120§</td>
<td>.305</td>
</tr>
</tbody>
</table>

Abbreviations. SD: Standard deviation; y: year; mo: month; CBCL: Child Behavior Checklist.
† Missing characteristics were unknown to parents.
‡ One CBCL questionnaire was not filled out.
§ Missing physical examination, because the child was too anxious to perform examination.
* Proportion children with CBCL T-score >63 (90th percentile).
Primary outcomes

Baseline data are presented in Table 1. Defecation frequency increased from an average of 2.0 stools per week to 7.2 in the CT group and 5.4 in the BT group at posttreatment (Table 2). Compared to the BT group, defecation frequency in CT was significantly higher (IRR=0.75, 95% CI=0.59-0.96; p=.021). Planned comparisons showed that this effect was mainly caused by a difference between interventions at posttreatment (7.2 vs. 5.4; p=.021), and not at follow-up (6.6 vs. 5.3; p=.150).

Fecal incontinence frequency dropped from an average of 15 per week at start of the study to 2.1 and 5.0 per week at posttreatment for respectively CT and BT (Table 2). From posttreatment to follow-up, fecal incontinence frequency increased to an average of 6.4 in CT and 8.6 in BT. There was no statistically significant difference found between treatment conditions (p=.135).

At posttreatment, success rate was higher in CT (62.3%) than in BT (51.5%) (Table 2). No statistically significant difference between treatments was found, though (p=.249). At follow-up, the number of children successfully treated declined to 57.3% in CT and 42.3% in BT. Again, the difference proved statistically non-significant (p=.095).

Table 2. The effect of treatment on primary outcome measures: defecation frequency, fecal incontinence frequency and the proportion of success.

<table>
<thead>
<tr>
<th></th>
<th>Conventional Treatment</th>
<th>Behavioral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Defecation frequency/week, mean (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posttreatment §</td>
<td>7.2 (6.1-8.5)</td>
<td>5.4 (4.3-6.7)</td>
</tr>
<tr>
<td>Follow-up *</td>
<td>6.6 (5.0-8.8)</td>
<td>5.3 (4.4-6.3)</td>
</tr>
<tr>
<td><strong>Fecal incontinence/week, mean (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posttreatment</td>
<td>2.1 (0.8-5.8)</td>
<td>5.0 (2.1-12.0)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>6.4 (3.5-11.7)</td>
<td>8.6 (4.0-18.3)</td>
</tr>
<tr>
<td><strong>Success, % (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posttreatment</td>
<td>62.3 (51.1-76.1)</td>
<td>51.5 (39.7-66.9)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>57.3 (46.6-70.4)</td>
<td>42.3 (31.8-56.4)</td>
</tr>
</tbody>
</table>

Abbreviations. CI: Confidence Interval; RR: Relative Risk, derived from generalized linear models for the binomial family with group (conventional treatment, behavioral therapy), defecation frequency and fecal incontinence frequency at baseline as factors in the model; IRR: Incidence Rate Ratio, derived from negative binominal regression models with group (conventional treatment, behavioral therapy), time (posttreatment, follow-up), the interaction term of group by time as factors and baseline score as covariate included in the model.
Secondary outcomes

Baseline data are presented in Table 1. Stool-withholding behavior was reduced from baseline to follow-up in both treatments conditions; from over two-third of the children withholding their stools to 13.8% in CT and 10.6% in BT at posttreatment (Table 3). The proportion of children with stool-withholding behavior did not differ between interventions (p=.654).

Most CBCL forms were filled out by mothers (72.3%), followed by fathers (15.4%) and others (10.8%) (i.e. stepmothers and stepfathers). In 59.6% of the full cases, the same responder filled out the CBCL at all assessment points with no difference between the two treatment groups (CT: 58.5%; BT: 60.7%, p=.813). Over one-third of the children exhibited behavior problems (CBCL T-score>63) at baseline. At end of treatment, this percentage was decreased to 22.8% in CT and 21.9% in BT (Table 3). At follow-up, BT was found to have influenced behavior problems significantly by reducing the proportion of children with these problems to 11.7% compared to 29.2% in CT (RR=0.42, 95% CI=0.18-0.96; p=.039).

The proportion of children with internalizing problems also declined from an average of 35.8% to 17.3% and 18.9% for respectively CT and BT (Table 3). At follow-up, this proportion increased in CT, but decreased further in BT (23.4%...
However, no statistically significant effect was found for the effect of treatment condition (p=.600), nor for the influence of behavioral therapy at follow-up (p=.156).

The proportion of children exhibiting externalizing problems changed from an average proportion of 26.9% to 15.9% in CT and 15.6% in BT at posttreatment (Table 3). Both treatments appeared equally effective in reducing externalizing problems (p=.990).

### DISCUSSION

This study is the first large randomized controlled trial evaluating the clinical effectiveness of behavioral therapy with laxatives for functional constipation in childhood. The results indicate that this behavioral therapy with laxatives has no advantage over conventional treatment in treating childhood constipation. Both treatments decreased fecal incontinence frequency and increased defecation frequency. However, conventional treatment resulted in a higher defecation frequency than behavioral therapy. Behavior problems were common with over one-third of the participating children exhibiting these problems. This study shows that behavioral therapy is superior in addressing behavior problems in constipated children.

<table>
<thead>
<tr>
<th>Table 3. The effect of treatment on secondary outcome measures: the proportion of children exhibiting stool-withholding behavior and behavior problems (CBCL T-score&gt;63).</th>
</tr>
</thead>
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<tr>
<td></td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Stool-withholding behavior, % (95% CI)</strong></td>
</tr>
<tr>
<td>Posttreatment $§$</td>
</tr>
<tr>
<td>Follow-up $*$</td>
</tr>
<tr>
<td><strong>CBCL Total score, % (95% CI)#</strong></td>
</tr>
<tr>
<td>Posttreatment</td>
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<tr>
<td>Follow-up</td>
</tr>
<tr>
<td><strong>CBCL Internalizing score, % (95% CI)#</strong></td>
</tr>
<tr>
<td>Posttreatment</td>
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<tr>
<td>Follow-up</td>
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<tr>
<td><strong>CBCL Externalizing score, % (95% CI)#</strong></td>
</tr>
<tr>
<td>Posttreatment</td>
</tr>
<tr>
<td>Follow-up</td>
</tr>
</tbody>
</table>

Abbreviations. CBCL: Child Behavior Checklist; CI: Confidence Interval; RR: Relative Risk, derived from generalized linear models for the binomial family with group (conventional treatment, behavioral therapy), time (posttreatment, follow-up), the interaction term of group by time, and the proportion of children having stool-withholding behavior or having CBCL T-score>63 at baseline as factors in the model.
Our results can only be compared with one other randomized controlled trial and one quasi-randomized trial, which also evaluated the effect of an extensive behavioral intervention with laxatives compared to conventional treatment. Borowitz et al. also found no differences in treatment success between three different treatment modalities: medical therapy, medical therapy plus enhanced toilet training and, medical therapy plus enhanced toilet training plus biofeedback training. Still, the enhanced toilet training intervention was considered to be more effective, since more children responded to treatment with decreases in fecal incontinence. This latter finding is in contrast with our outcome. Taitz and colleagues investigated in 47 children the additional effect of play therapy with both a focus on the individual child and on parent-child interaction. In accordance with our results, their findings indicated that psychotherapeutic elements do not add to medical treatment, which traditionally already incorporates behavioral management techniques such as toilet training, positive reinforcement and education.

Our hypothesis that behavioral therapy would result in more children ceasing their stool withholding behavior than conventional treatment was not confirmed. The main assumption underlying our behavior therapy was that fear for defecation perpetuates chronic constipation with stool-withholding behavior as avoidance response. Prescribed laxative treatment may have been less effective in our study compared to the intervention groups, which may explain the lack of difference in stool-withholding behavior.

<table>
<thead>
<tr>
<th>Group†</th>
<th>Group x Time‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR=0.77</td>
<td>95% CI=(0.24-2.46)</td>
</tr>
<tr>
<td>p=.654</td>
<td></td>
</tr>
<tr>
<td>RR=1.04</td>
<td>95% CI=(0.65-1.68)</td>
</tr>
<tr>
<td>p=.863</td>
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</tr>
<tr>
<td>RR=1.16</td>
<td>95% CI=(0.66-2.03)</td>
</tr>
<tr>
<td>p=.600</td>
<td></td>
</tr>
<tr>
<td>RR=1.00</td>
<td>95% CI=(0.52-1.90)</td>
</tr>
<tr>
<td>p=.990</td>
<td></td>
</tr>
</tbody>
</table>

† Group: the main effect of behavioral treatment on CBCL score.
‡ Group x Time: the interaction effect of behavioral treatment with CBCL score at follow-up.
§ Posttreatment: assessment of clinical outcomes at the last treatment visit.
* Follow-up: assessment of clinical outcomes 6 months after the 22-week treatment was ended.
# Proportion children with CBCL T-score >63 (90th percentile).
caused large improvement of this aberrant behavior in both interventions. Laxatives facilitate transport and expulsion by softening of stools and thus seem to prevent stool-withholding behavior sufficiently \(^8\), \(^17\).

Conventional treatment was associated with more frequent bowel movements per week. Before starting treatment, optimal laxative dosages were established for each child by the pediatric gastroenterologists. However, during behavioral therapy pediatric psychologists adjusted laxative dosages and only consulted the pediatric gastroenterologist when necessary in their opinion. This possibly resulted in prescribing suboptimal dosages and less use of rescue medication. This stresses the important role for experienced pediatricians in regulating laxatives, one of the main components in the treatment of childhood constipation \(^30\).

As expected behavioral therapy relieved more children from coexisting behavior problems. This is not surprisingly, since the behavioral protocol aims at decreasing anxiety and teaches parents behavior modification procedures. Part of the reduction in behavioral problems may be explained by normalized behavioral functioning after successful treatment, since it is assumed that the social impact of fecal incontinence is mainly responsible for disturbed behavior in children with functional defecation disorders \(^31\)-\(^33\). The exact relationship between functional constipation and behavior problems still remains unclear though, as well as the influence of behavior problems on treatment outcome. Since in this study no difference in success rate was revealed between the two intervention arms, the beneficial effect of behavioral therapy on behavioral functioning seems not to be (directly) related to resolution of constipation-related symptoms.

Some limitations of this study need to be considered. The visit frequency and duration of treatment of the conventional treatment were made equivalent to that of the behavioral treatment group to strengthen the comparison of treatments, which however could also jeopardize generalizing the findings to general practice. Regardless of high visit frequency and duration this did not lead to a higher success rate compared to those studies with two to six visits in a time period of six months, though \(^18\), \(^26\), \(^31\), \(^32\), \(^34\), \(^35\). Generalization of the findings may also be hampered as the pediatric gastroenterologists involved in this study are highly specialized and experienced in treating chronic constipation. However, conventional treatment in our study was based on the clinical practice guideline from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) \(^36\) that provides recommendations for management of functional constipation by the primary care provider. These guidelines are generally available and employed by many pediatric gastroenterologists and primary care providers. Furthermore, primary
outcome measures and stool-withholding behavior were not blindly rated. Another limitation was that pediatric psychologists were partly responsible for laxative treatment in the behavioral therapy condition, which possibly resulted in differences in laxative treatment. Despite the afore-mentioned limitations, we feel that our study has several strong points such as a large sample that approximates the average patient in primary care settings with no restrictions regarding psychiatric abnormalities. Furthermore, two well-controlled and protocolized specialized treatments were used with similar frequency of visits and a 6-months follow-up period. Also, this study showed a low attrition rate. This randomized controlled trial showed that behavioral therapy with laxatives has no advantage over conventional treatment in treating childhood constipation. Conventional treatment should remain the first choice of treatment. Behavioral therapy may be considered when children experience behavior problems concurrently. Quality of care for chronically constipated children may be improved by adding a behavioral screening to the clinical evaluation of constipated children \(^{13, 36}\). Positive screening should lead to considering behavioral therapy or referral to mental health services.

Acknowledgements

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REFERENCES


Chapter 3

Application of rectal enemas in children with severe constipation: a randomized controlled trial

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Submitted
ABSTRACT

Background & Aims
Treatment of childhood constipation is often long-lasting. After 5 years of intensive oral laxative use, up to 30% of constipated children still have unsuccessful outcome. Children refractory to oral laxatives may benefit from regular rectal evacuation by enemas. This randomized controlled trial aimed to compare clinical effectiveness of additional treatment with rectal enemas (intervention) to conventional treatment alone (control) in severely constipated children.

Methods
In a tertiary hospital in the Netherlands 100 children, aged 8-18 years, with functional constipation for at least 2 years were randomized to either intervention or control. The control group received education, behavioral strategies and oral laxatives. In addition, intervention consisted of 3 rectal enemas/week reduced by 1 enema/week every 3 months. Outcome measures were defecation and fecal incontinence frequency and overall success at 12, 26, 39 and 52 weeks. Overall success was defined as ≥3 defecation/week and <1 fecal incontinence episode/week, irrespective of laxative use.

Results
Defecation frequency normalized in both groups, but was significantly higher in the intervention group compared to control at 26 and 52 weeks (5.6 vs 3.9/week, p=0.02, and 5.3 vs 3.9/week, p=0.02, respectively). There were no significant differences, however in reduction of fecal incontinence episodes (p=0.49) and overall success rates (p=0.67) between the treatment groups. After one year of treatment, overall success rate was 47.1% in the intervention group versus 36.1% in the control group.

Conclusions
There is no additional effect of rectal enemas compared to oral laxatives alone as maintenance therapy for severely constipated children.
INTRODUCTION

Treatment of pediatric functional constipation is challenging. Studies in constipated children show an insufficient response to conventional treatment (education, bowel diary, toilet training and oral laxatives) and relapses are common\(^1,2\). After one year of intensive conventional treatment approximately 30-40% of children with functional constipation still have a low defecation frequency and suffer from fecal incontinence\(^3,4\). Moreover, long-term follow-up studies showed similar percentages of persistence of functional constipation in children\(^1,2,5,6\). Constipation and secondary fecal incontinence are a source of distress and concern for the child and its family. Physical complaints, such as painful defecation and abdominal pain associated with constipation, and long duration of symptoms may result in impaired quality of life, reported by both child and parents\(^7\).

Conventional treatment generally consists of education of the child and parents, demystification of constipation, dietary advice, behavioral modification and administration of laxatives\(^8-10\). Laxative therapy comprises two phases: disimpaction with oral or rectal laxatives when fecal impaction is present and maintenance therapy with oral laxatives for several months\(^9,10\). Failure of conventional treatment may be caused by poor adherence to treatment, but could also result from the fact that conventional treatment is not addressing the underlying pathophysiology.

Refractory constipation is characterized by recurrent fecal impaction\(^11\). Mechanisms leading to repetitive accumulation of feces in the rectum may be retentive posturing of the child, anal sphincter dyssynergia, abnormal rectal function or motility disorders of the colon\(^11-13\). A recent study found that an increased rectal compliance (i.e. the capacity to stretch upon a pressure stimulus) was a predominant feature in the majority of constipated children\(^13\). Due to a higher rectal compliance these children require larger stool volumes to trigger sensation of urge to defecate, contributing to longer intervals between defecation. Longer intervals between defecation result in hard stools, subsequently leading to difficulties in stool evacuation and eventually in fecal impaction. Based on these findings we hypothesize that children refractory to oral laxatives may benefit from regular rectal evacuation by enemas. Therefore, the aim of this study was to demonstrate whether additional treatment with rectal enemas is clinically more effective than conventional treatment alone in severely constipated children.
METHODS

Study participants

Children were recruited from a specialized outpatient clinic for functional defecation disorders at the Department of Pediatric Gastroenterology of the Emma Children’s Hospital/AMC in Amsterdam, the Netherlands. All children between 8 and 18 years with functional constipation were eligible for enrollment. Functional constipation was defined as presence of at least 2 of 4 of the following symptoms: 1) spontaneous defecation frequency <3 per week, 2) fecal incontinence episodes ≥2 per week, 3) passage of large diameter stools that may obstruct the toilet and 4) palpable abdominal or rectal mass on physical examination. Only children who had symptoms of functional constipation for at least 2 years and were unresponsive to conventional treatment were included. Children who had been treated with enemas on a regular basis (more than 3 rectal enemas in previous treatment) were excluded from the study. Furthermore, children with organic causes of constipation, including Hirschsprung’s disease, muscle disorders, prior recto-anal surgery, spina bifida, mental retardation or hypothyroidism were excluded. All subjects and/or parents gave informed consent. The study protocol was approved by the medical ethical committee of the Academic Medical Centre of Amsterdam.

Study Design

The study had a randomized controlled design and consisted of two parallel treatment groups: conventional treatment (control group) or conventional treatment combined with regular application of rectal enemas (intervention group). After baseline measurement and if written informed consent was given, the physician performed a telephone call to a randomization centre and revealed the allocation to the child and parents immediately. A computer-based system was used to generate a sequence of random group assignment for consecutive patients. This computer program used minimization to achieve a balanced randomization on two factors: gender and age (<13 years versus ≥13 years).

Baseline assessment

To verify eligibility for enrolment and to obtain baseline data assessment, children and parents were asked to record defecation and fecal incontinence frequency, passage of large amount of stools, painful defecation and abdominal pain in a diary one week prior to entry. In all patients, laxative treatment was discontinued during this week. At entry, a standardized interview was
Conducted to determine defecation pattern including defecation frequency, stool consistency, painful defecation, fecal incontinence episodes, abdominal pain and stool withholding behavior. Abdominal and rectal examination was performed to evaluate presence of fecal impaction.

**Treatment strategies**

At start of treatment, all children underwent rectal disimpaction by rectal enema (120 ml sodium-dioctylsulfosuccinate and sorbitol) on three consecutive days. If rectal disimpaction was unsuccessful, rectal enemas were continued for a maximum of seven days. Conventional treatment consisted of education, behavioral strategies and oral laxatives. Patients were instructed to start toilet training three times daily after each meal and not to withhold stool when they felt urge to defecate. Parents were advised to apply a non-accusatory approach. Motivation was enhanced by praise and small gifts. Oral laxative therapy consisted of polyethylene glycol with a starting dose of 0.5 g/kg. If treatment was considered insufficient the dose was increased until success was achieved. In the control group, a rectal enema or bisacodyl suppository of 5 mg was only prescribed in case of reoccurrence of fecal impaction. In the intervention group, children received 3 rectal enemas weekly during the first 3 months. Thereafter this frequency was reduced by 1 enema per week every 3 months.

**Follow-up and outcome measures**

In both treatment groups, patients kept a bowel diary to record daily defecation frequency and fecal incontinence episodes, painful defecation, abdominal pain and laxative use. Visits to the outpatient clinic for evaluation of defecation pattern and laxative use were scheduled for all children at 2, 4, 6, 12, 26, 39 and 52 weeks. In addition, at week 52, subjective feelings about application of rectal enemas were assessed. Children in the intervention group filled out the following four questions, derived from a previously developed health-related quality of life questionnaire 15: Question 1: After application of rectal enema I have stomach ache; Question 2: After application of rectal enema I am feeling worse; Question 3: Application of rectal enema is important to solve my defecation disorder; and Question 4: I find the application of a rectal enema terrible. Answers were based on a five point Likert scale.

Main outcome measures were defecation frequency per week, fecal incontinence frequency per week, and overall treatment success after 12, 26, 39 and 52 weeks of treatment. Overall success was defined as ≥3 bowel movements per week and <1 fecal incontinence episode per week, irrespective
of laxative use. Secondary outcome measures were abdominal pain and painful defecation at 12, 26, 39 and 52 weeks, and scores on the short questionnaire about regular application of rectal enemas after one year of treatment.

Statistical Analysis

Clinical symptoms of functional constipation at baseline are presented in a descriptive manner. In general, our outcome data consisted of repeated measurements over time in the same patient, and therefore we applied models that explicitly take into account the correlation that is likely to exist between measurements within the same individual.

To study defecation frequency (continuous variable) over time, we used a linear mixed model that contained: treatment (control vs. intervention), time (categorical with 4 levels), baseline measurement (continuous) and the interaction between treatment and time. No mathematical pattern was imposed on the covariance structure for measurements within the same individual (unstructured). Mixed model analysis has the advantage that data from all available visits are used in analysis, and not only the complete cases.

To examine whether one treatment was more effective than the other, we first performed a single overall test which jointly tested whether the differences in outcomes between the two treatment groups at all 4 follow-up visits were zero (e.g. both treatment are equally effective). Only if the overall test was significant, we tested for differences in outcomes at specific time points to avoid the problem of multiple testing.

Generalized estimation equation (GEE) models were used to analyze trends over time in binary outcomes (defecation frequency <3 per week or ≥3 per week, fecal incontinence frequency <1 per week or ≥1 per week, clinical success yes/no, abdominal pain yes/no, painful defecation yes/no). GEE models are an extension of generalized linear models in order to deal with correlated outcomes. Within the GEE framework, a working correlation matrix is estimated to adjust the standard parameters for the correlation that is present. Again, the working correlation matrix was considered unstructured. GEE models were similar in nature as the mixed models and also contained: treatment given, time categorical, and the interaction between treatment and time.

Prior to the study a sample size calculation was made expecting a 30% difference in the proportion of success between control and intervention. It was estimated that conventional treatment reached success in 30% of the children after one year of treatment. Under the additional assumption of a significance level of 0.05 with a power of 0.80, and 2-sided hypothesis testing, a minimal sample size of 84 with 42 children in each group was required. Statistical analyses
were performed by using SPSS windows version 12.0.2 (SPSS Inc., Chicago, Illinois, USA) or SAS version 9.1 (SAS Institute Inc., Cary, North Carolina, USA). Statistical significance was accepted at \( p < 0.05 \). This trial is registered as an International Standard Randomized Clinical Trial, number ISRCTN 99089299. There was no external funding source.

RESULTS

Patients

Between September 2001 and November 2005 a total of 102 children referred by general practitioners, school doctors, and pediatricians enrolled in the study (figure 1). Fifty-one patients were allocated to the intervention group and 51 to the control group. Two randomized patients never commenced their allocated therapy and were therefore excluded from the analysis. A total of 87 patients completed the trial, while 13 patients (control \( n=7 \) and intervention \( n=6 \)) terminated the trial prematurely (figure 1). All those patients remained in the analysis. In November 2006, one year follow-up of the last included patients was completed.

Of the 100 patients who started with allocated treatment, 65 were boys, the median (25th–75th percentile) age at baseline was 10.7 (9.4-12.3) years and the median duration of symptoms was 6.9 (5.0-9.2) years. A defecation frequency of \(<3/week\) was found in 84% and fecal incontinence episodes \( \geq 2/week \) in 82% of all patients. Baseline characteristics for the two treatment groups are presented in table 1.

Treatment adherence

Six patients randomized to the strategy control switched to the intervention strategy as their response to oral laxative therapy was insufficient. This switch to the other treatment arm occurred at week two in 2 patients, at week 6 in 1 patient, at week 18 in 2 patients and at week 26 in 1 patient. These patients were considered as treatment failures in the control group, and analyzed as such. Furthermore, 11 control patients needed short-term disimpaction treatment, i.e. rectal enemas or bisacodyl suppositories for 1 to 3 days, during the trial period. Fecal impaction reoccurred once in 5 patients, while 6 patients needed disimpaction twice for separate episodes. In 7/11 (64%) of these patients, fecal impaction reoccurred in the first 6 weeks after starting conventional treatment. None of the patients switched to rectal laxatives on a regular basis, and were therefore not considered as treatment failures. Two patients assigned to the
intervention group responded unsatisfactorily to regular rectal enemas and switched to daily rectal lavage with tap water. These patients were considered as treatment failures in the intervention group. In 7 children rectal enemas were stopped in advance of the predetermined scheme as they reached successful outcome, while 4 patients refused further application of rectal enemas although they still exhibited symptoms of constipation (two in the first 12 weeks and two between 27-39 weeks).

**Main outcome measures**

The results of the intention-to-treat analyses of the main outcome measures based on all 100 patients are shown in figures 2, 3 and 4. Compared to baseline an increase in defecation frequency is seen for both the intervention and control group (figure 2). The overall test showed a significant difference in defecation frequency between the two groups (p=0.01). Defecation frequency was significantly higher in the intervention group compared to the control.
group at 26 and 52 weeks (modeled mean frequency per week 5.6 vs 3.9/week, 
p=0.02, and 5.3 vs 3.9/week, p=0.02, respectively). In addition, a defecation 
frequency of <3 per week was more often present in the control group than 
the intervention group during the trial period, but the overall test showed no 
significant difference between groups (p=0.27).
At baseline, fecal incontinence frequency <1 per week was reported in 14% 
and 10% of children in the control group and intervention group, respectively. 
Fecal incontinence frequency decreased during the trial period (figure 3). The 

Table 1. Baseline characteristics per randomized group*

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Male gender</td>
<td>33/50 (66)</td>
<td>32/50 (64)</td>
</tr>
<tr>
<td>Age at baseline, yrs</td>
<td>11.0 (9.5-12.5)</td>
<td>10.5 (9.2-11.8)</td>
</tr>
<tr>
<td>Age at onset of constipation, yrs</td>
<td>4.0 (3.0-5.0)</td>
<td>4.0 (3.0-5.0)</td>
</tr>
<tr>
<td>Duration of symptoms, yrs</td>
<td>7.0 (5.1-9.3)</td>
<td>6.5 (4.7-9.3)</td>
</tr>
<tr>
<td>Defecation frequency / week</td>
<td>1.0 (0.0-2.5)</td>
<td>1.5 (0.4-2.5)</td>
</tr>
<tr>
<td>Defecation &lt;3 /week</td>
<td>44/50 (88)</td>
<td>40/50 (80)</td>
</tr>
<tr>
<td>Fecal incontinence frequency / week</td>
<td>7.0 (2.4-14.0)</td>
<td>7.5 (3.0-10.3)</td>
</tr>
<tr>
<td>Fecal incontinence ≥2 /week</td>
<td>39/50 (78)</td>
<td>43/50 (86)</td>
</tr>
<tr>
<td>Large amount of stools</td>
<td>35/50 (70)</td>
<td>37/50 (74)</td>
</tr>
<tr>
<td>Stool withholding behavior</td>
<td>29/49 (59)</td>
<td>33/48 (69)</td>
</tr>
<tr>
<td>Abdominal / Rectal fecal impaction</td>
<td>27/49 (54)</td>
<td>25/50 (50)</td>
</tr>
</tbody>
</table>

* depicted as proportion (%) or median (25th - 75th percentile)

...
percentages of children with <1 fecal incontinence episodes per week were not significantly different between the two treatment groups (p=0.49). Overall treatment success was not significantly different between intervention and control during the trial period (p=0.67). After one year treatment, 47.1% of patients in the intervention group was successful compared to 36.1% in the control group (figure 4).

Relationship between defecation frequency and fecal incontinence episodes
At baseline, all children presenting with a defecation frequency <3 per week showed a wide range of fecal incontinence episodes from 0 to 42 times per week. After one year of intensive monitoring and treatment, 83% (72/87) of all children had a normalized defecation frequency. Fifty percent of these children (36/72) still experienced weekly fecal incontinence, ranging from 1 to 14 episodes per week.

Secondary outcome measures
At baseline, abdominal pain and painful defecation were present in respectively 69.4% and 60.4% in the intervention group versus 78.0% and 52.0% of children in the control group. Pain decreased during treatment in both groups and no statistical significant difference was found between the two groups (table 2). Children in the intervention group, who filled out a short questionnaire after one year, indicated that abdominal pain after a rectal enema was present: never/
seldom in 39%, sometimes in 31% and often/always in 30%. Children felt worse after application of a rectal enema: never/seldom in 76%, sometimes in 11% and often/always in 13%. Thirty-eight percent of children thought that rectal enemas were not at all or only a little important to solve their defecation disorders, 20% found it quite important, and 42% rated it as very to extremely important. A rectal enema was perceived as very to extremely terrible in 15% of children, while 11% reported it as quite terrible and 74% found it no problem at all.

Figure 4. Overall success for both treatment groups
*Overall test for differences between intervention and control at all four time points using GEE analysis.

Table 2. Percentages (%) of children with abdominal pain and painful defecation in both treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>78,0</td>
<td>69,4</td>
</tr>
<tr>
<td>Week 12</td>
<td>29,7</td>
<td>25,6</td>
</tr>
<tr>
<td>Week 26</td>
<td>38,9</td>
<td>19,6</td>
</tr>
<tr>
<td>Week 39</td>
<td>26,6</td>
<td>15,7</td>
</tr>
<tr>
<td>Week 52</td>
<td>30,6</td>
<td>20,3</td>
</tr>
<tr>
<td>Painful defecation (%)#</td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>52,0</td>
<td>60,4</td>
</tr>
<tr>
<td>Week 12</td>
<td>16,2</td>
<td>13,8</td>
</tr>
<tr>
<td>Week 26</td>
<td>18,0</td>
<td>11,4</td>
</tr>
<tr>
<td>Week 39</td>
<td>19,3</td>
<td>17,0</td>
</tr>
<tr>
<td>Week 52</td>
<td>20,9</td>
<td>8,8</td>
</tr>
</tbody>
</table>

*p=0.36; #p=0.35 (Overall test for differences between control and intervention at all time points using GEE analysis).
DISCUSSION

This is the first randomized controlled trial investigating the role of rectal enemas as maintenance treatment of childhood constipation. Rectal enemas were well tolerated, but regular enema administration led to no clinical benefit compared to oral laxatives alone in children with severe constipation. Overall, children in the intervention group had a significantly higher defecation frequency compared to the control group after six months and one year of treatment. Nevertheless, the clinical relevance of this finding is questionable, as mean defecation frequency improved to a normal frequency in both groups at all evaluation moments. Yet, persistent low defecation frequency after one year treatment was still present in a subgroup of children (control group 30.2% versus intervention group 12.6%, p=0.05). Those children may suffer from a colonic dysmotility due to neuromuscular abnormalities, which was earlier recognized in adults and children with intractable constipation 19-23. Discussion remains whether pediatric refractory constipation reflects a true intrinsic gut anomaly causing slow-transit constipation or results from an acquired motility disorder after years of severe functional constipation 24, 25. More fluctuation in defecation frequency within the normal range was seen in the control group. This could be the result of earlier reduction and/or discontinuation of oral laxatives. In this group, oral laxatives were reduced after three to four months if children exhibited regular bowel movements, probable resulting in a slight decrease in defecation frequency at six months. In response, adjustment of oral laxatives dosage led to an increase in mean defecation frequency at nine months, while again at one year a decrease was seen. At that moment 37.2% of children in the control group were off laxatives compared to 29.5% in the intervention group. A more constant defecation frequency in the intervention group was likely resulted from the fact that in the first nine months only rectal enemas, and not oral laxatives, were reduced in a step-by-step manner. Abdominal pain and painful defecation, possible side effects of rectal enemas, were not more frequently reported by children in the intervention group. Self-report of the children underlined that the vast majority of children did not experience rectal enemas as terrible. These findings contradict the general belief that application of rectal enemas is traumatic for children and need to be avoided as much as possible. Limited improvement in fecal incontinence frequency was seen during one year of treatment. Even the regular application of rectal enemas had no additional positive effect. Approximately half of all children continued to experience one or more episodes of fecal incontinence per week, despite a normal defecation frequency in the majority of these children. Fecal incontinence associated
with constipation is thought to be secondary to fecal impaction, either as involuntary overflow incontinence or as stool leakage from the rectum as feces approaches the anus. Therefore, persistence of fecal incontinence in children with successful disimpaction and a normal defecation frequency is more difficult to understand. Fecal continence is maintained by involuntary and voluntary muscle contractions, the latter depending on the perception of rectal distention. Diminished perception of rectal distention, i.e. rectal hyposensitivity, has been reported in both children and adults with constipation and fecal incontinence. Rectal hyposensitivity can be caused by either abnormal rectal wall properties (e.g. compliance, tone or contractility) or impaired afferent pathway function (e.g. impaired mechanoreceptors, afferent nerve sensitivity or defect central processing). Recent studies showed that abnormal thresholds for sensation were only present in 5-10% of constipated children, while rectal compliance was increased in approximately two third of these children. As a result of elevated rectal compliance, greater rectal volumes are required to elicit sensory thresholds without change in afferent nerve sensitivity.

Nevertheless, constipated children with fecal incontinence often report “loss of sensation of stool in the rectum” or “late recognition of stool in the rectum and a sense of extreme urgency”. It could be hypothesized that an interaction between sensory and behavioral/psychosocial factors plays a role in persistence of fecal incontinence. In general, stool withholding behavior upon urge to defecate is thought to play a role in the development and/or persistence of constipation in most children. In our study, postponement of defecation was indeed reported in 64% of all children at intake. Regarding the onset of constipation around the age of four years, we speculate that these children displayed stool withholding behavior for many years. This habitual behavior to ignore the defecatory urge may still be present in a subgroup of children, despite regular defecation without pain and hard stools, and result in persistence of fecal incontinence. Furthermore, although sensory testing with rectal barostat revealed no abnormalities in the majority of children, in daily life, children suffering from fecal incontinence may be less aware of rectal sensations when distracted by playing games or watching TV.

Disappointing low success rates were found in our study population compared to one-year success rates of 60-70% in previous studies. This underlines that our study population represents children with severe functional constipation. To develop better treatment strategies for these children better understanding of the multifactorial etiology is needed. To date, novel therapies, such as new classes of drugs, electrical sacral nerve/transcutaneous stimulation or botulinum toxin injection, are potential helpful.
when conventional treatment fails. Moreover, there is increasing interest in alternative therapies, like acupuncture or hypnosis, which may benefit children with functional gastrointestinal disorders refractory to standard treatment. Evidence for efficacy of these novel treatments is mainly based on small clinical trials, mostly in adults, and needs to be confirmed by well-designed randomized studies in constipated children.

A limitation of this study is that 13% of children dropped out during one year treatment and 8% switched treatment. The drop-out rate was not different between the two treatment groups, hence most likely of limited effect on the results. However, overall success rate could be biased by the fact that drop-outs may have been more severely constipated compared to the children that completed the study. We tried to minimize this bias by using the described linear mixed model and generalized estimation equation in which not only the children that completed the trial, but all cases were included. In the analysis we further corrected for deviation from randomized allocation, as all switchers were analyzed in their original randomized group but considered as treatment failures. Ideally switching needs to be avoided in randomized clinical trials, but this type of deviation would also occur in routine practice.

In conclusion, this randomized controlled trial showed that application of rectal enemas on a regular basis was well tolerated, but had no additional effect on conventional treatment with oral laxatives for severely constipated children. Therefore, there is no place for rectal enemas in the maintenance therapy in these severely constipated children. Rectal enemas should only be used for initial disimpaction.
REFERENCES


Rectal enemas for severe childhood constipation


Part II

Prognosis of functional constipation
Chapter 4

Functional constipation in children: A systematic review on prognosis and predictive factors

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Marc A. Benninga
Marjolein Y. Berger

Submitted
ABSTRACT

Background
Knowledge on prognosis and factors influencing the clinical course of functional constipation in children is important to enable general practitioners and paediatricians to give accurate patient information, to weigh treatment strategies and identify children with high-risk for unfavourable outcome.

Objective
To investigate and summarize the quantity and quality of current evidence on prognosis of childhood constipation with and without treatment and its predictive factors.

Methods
An extensive literature search in Medline and Embase was performed to identify prospective follow-up studies evaluating the prognosis or prognostic determinants of functional constipation. Methodological quality was assessed using a standardized list. Results on prognosis of constipation were statistically pooled, and the influence of prognostic factors was summarized in a best evidence synthesis.

Results
The search strategy resulted in a total of 2386 abstracts. Only 19 publications met our inclusion criteria, of which 23% scored high methodological quality. Included studies showed large heterogeneity in study populations and outcome measures. With disregard of these differences, 58.9±20.2% of all children followed for 6-12 months was recovered and off laxatives. Six studies showed that at the end of follow-up, 13.9±6.6% of recovered children were still using laxatives. There is substantial evidence that defecation frequency and a positive family history are not associated with recovery of constipation.

Conclusion
The few studies published on prognosis of childhood functional constipation and predictive factors showed large heterogeneity and poor methodological quality. Overall, 58.9% of children are found to recover after 6-12 months. Recovery rate showed no relation with defecation frequency or positive family history. Based on the current literature, we are unable to identify a group of children with high-risk for poor prognosis.
BACKGROUND

In childhood, functional constipation is a common complaint. In the general population prevalence is reported to vary from 0.7 to 29.6% \(^1\). This large variation may be due to lack of a generally used definition to classify constipation. Consensus is hampered by the fact that clinical presentation is divers and pathophysiology is multifactorial. Even though several internationally accepted guidelines such as NASPGHAN\(^2\), PACCT\(^3\) and recently Rome III\(^4\) have been developed to provide criteria for constipation, none of them have been worldwide implemented in research or clinical practice yet.

There are different concepts on the clinical course of constipation in children. Some authors suggest that constipation is a constitutional condition which gradually disappears \(^5\). Others find that despite intensive therapy 30-50% percent of the children persist to have severe symptoms after 5 years of follow-up \(^6,7\).

Knowledge on factors influencing the clinical course of functional constipation in children is important to enable general practitioners and paediatricians to give accurate patient information, to weigh treatment strategies and identify children with high-risk for unfavourable outcome. However, no overview of these prognostic factors exists in current literature. Therefore our aim was to investigate and summarize the quantity and quality of the current evidence on the course of constipation in children with and without treatment, and determinants that predict this course.

METHODS

Search strategy

The Medline database was searched from 1965 to March 2008, and EMBASE from 1980 to April 2007. The keywords (medical subheadings (MeSH) and text words) used to describe constipation were: “constipation”, “obstipation”, “coprostasis”, “encopresis”, and “soiling”. The study population was identified by the words: “child”, “infant” and “adolescent”. For Medline the following query was added: (incidence[MeSH] OR follow-up studies[MeSH] OR prognosis OR predict*[Text Word] OR course*[Text Word] OR Epidemiologic Studies). For EMBASE we combined the search with the strategy for detecting prognostic studies recommended by Wilczynski et al. \(^8\). In addition, reference lists of review articles and included studies were searched. No language restriction was applied.
Two reviewers independently screened all abstracts of identified published articles for eligibility. For this purpose, four inclusion criteria were used: 1) study population consisted of children between 0 to 18 years of age; 2) a prospective observational study design; 3) one of the aims of the study was to evaluate the prognosis of functional constipation expressed as duration or recurrence of functional constipation and determinants that influence prognosis; 4) follow-up was at least 8 weeks.

Excluded were papers concerning children with mental handicaps or psychiatric diseases (i.e. eating disorders), as well as studies investigating children with organic causes of constipation and children with functional non-retentive faecal incontinence.

All potentially relevant studies, as well as the studies of which the abstracts didn’t provide sufficient information for in- or exclusion, were retrieved as full papers.

Any disagreements regarding the inclusion of articles were resolved through consensus when possible or by arbitration of a third person.

Quality assessment

To assess methodological quality of the included studies we developed a standardized list (Table 1). We modified an established criteria list used in systematic reviews of prognostic studies 9-12. Two reviewers independently rated the methodological quality with the 15 items of the quality score list. Each of the items had an answer option of ‘yes’/’no’/’unclear’ (i.e. insufficient information). A score of 1 point was given only to a criterion that is assessed with ‘yes’. Equal weights were applied to all items, resulting in a maximum score of 15 points. Disagreements were resolved through consensus or by arbitration of a third person.

Data extraction

Two reviewers independently performed a structured data extraction from the original reports. Extracted information included (if available) items referring to setting, participants (diagnosis, age, gender, withdrawal/dropouts), interventions and outcome measures. Disagreements were resolved by consensus or by arbitration of a third person.

Data analysis

Inter-assessor reliability on methodological quality was calculated using kappa-scores 13. Our primary outcome was recovery of constipation as defined
Prognosis and predictive factors of childhood constipation

by the authors of the papers. Large clinical diversity among included studies with regard to participants, disease definitions and definition of outcomes existed. Furthermore, different statistical approaches and adjustments for different variables were used. Nevertheless results on prognosis of constipation were pooled using stratification to overcome large differences in duration of follow-up, study quality and setting.

We refrained from statistically pooling of results with regard to prognostic factors \(^1\), but carried out a best evidence synthesis for associations with recovery from constipation. Using the methodological quality list, quality scores were calculated as a percentage of the maximum score. High quality is defined as a score of 60% or more of the maximum score (i.e. a score of \(\geq 9\) points).

In the best evidence synthesis, evidence was divided in the following levels: 1) Strong: consistent findings (\(\geq 75\%\) of the studies report consistent findings) in at least 2 high quality studies; 2) Moderate: consistent findings in one high

Table 1. Methodological quality list

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<th>Study population</th>
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<td>1. Inception cohort</td>
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<td>2. Description of study population at least mentioned are: setting; age; duration of constipation; severity of constipation (described as defecation frequency or presence of faecal incontinence)</td>
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<td>3. Description of in- and exclusion criteria</td>
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<td>4. Description of setting</td>
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<td>Follow up</td>
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<td>5. Prospective data collection</td>
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<td>6. Follow up of at least 12 months</td>
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<td>7. Loss to follow up &lt; 20 %</td>
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<td>8. Information about loss to follow up</td>
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<td>Outcome</td>
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<td>9. Standardized measurement of outcome (baseline and FU identically measured)</td>
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<td>10. Independent measurement of outcome (blinded for prognostic factors)</td>
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<td>Prognostic factors</td>
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<td>11. Presentation of prognostic factors at baseline. (At least mentioned are age, gender, duration of constipation and severity of constipation)</td>
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<td>12. Standardized measurement of prognostic factors (baseline and FU identically measured and presented)</td>
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<td>13. Independent measurement of prognostic factors (blinded for outcome)</td>
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<td>Analysis</td>
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<td>14. Measure of association and measures of variance given</td>
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<td>15. Multivariate analysis used</td>
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quality cohort and at least 2 low quality studies; 3) Limited: findings of one high quality cohort or consistent findings in at least 3 low quality studies; 4) Conflicting: inconsistent findings (<75% of the studies report consistent findings); 5) Insufficient: no high quality studies and less than 3 low quality studies available. The level of evidence was based on the results in high quality studies only in case ≥2 high quality studies were available. Only statistically significant associations are considered as associated prognostic factors in this synthesis.

RESULTS

Included studies

The search strategy resulted in a total of 2386 abstracts. After eligibility screening 19 publications were judged potentially relevant. After reading the full text articles, 6 studies were excluded, because the study design was not a prospective observational study, but based on a retrospective chart review or a cross-sectional survey. Only three studies were not published in English, but in Polish and Spanish. These papers were translated. Full characteristics of the included studies are described in Table 2 (see Appendix).

Setting

Of the 13 included studies, six were conducted in a general paediatric department, six in a paediatric gastroenterology department and in one paper no setting was stated. None of the included studies were conducted in a primary care centre.

Outcome measures

All studies described a composed definition of recovery, resolvement or successful treatment of constipation as positive outcome, except for two studies that did not specify their outcome. Definitions of outcome measures varied strongly, nevertheless all studies took into account defecation frequency: in one study, having more than four bowel movements per week was a requirement for success, all other studies applied the criterion of at least three bowel movements per week. Frequency of fecal incontinence was included in the success definitions of eight studies: in five studies the success definition required less than two episodes per month, one study allowed one episode per two weeks, and in two studies children were not allowed to have any fecal incontinence. No abdominal pain or no pain with defecation was included in the success definition of three studies. All studies but four took laxative use into account in their definition of success, and six studies presented recovery rates of children off laxatives and children still using laxatives.
Study population In total 1680 children participated in the included studies. Age was reported in mean\textsuperscript{16,18,22-27} (mean 71.7±38.0 months) or median\textsuperscript{6,7,17,30,31} (range 3.5 to 100.8 months). Distribution of gender of all randomised children was reported in all studies but two\textsuperscript{18,23}: 50.9\% of participants were boys (M/F 782/752). Duration of constipation before start of the study was reported in 11 papers (expressed in mean or median duration before start of the study\textsuperscript{7,16,18,30}, mean or median age of onset\textsuperscript{17,24,26,27}, or defined in the inclusion criteria\textsuperscript{6,22,31}). Two studies did not report duration\textsuperscript{23,25}. Numbers on severity of constipation at baseline (e.g. defecation frequency, frequency of faecal incontinence episodes, presence of abdominal pain) were not presented in 3 studies\textsuperscript{18,25,26}. All other included studies used symptoms of constipation to express severity of constipation.

Follow-up time Most papers expressed follow-up time in mean number of months (mean: 2.75±24.79 months). Two studies presented follow-up time in median number of months\textsuperscript{7,30}, and one study presented a range\textsuperscript{22}.

Methodological quality
The three reviewers (MP, MBo and MYB) initially agreed on 85.6\% of the items of the methodological quality list. Inter-observer reliability of methodological quality assessment (0.71) was high. Overall methodological quality score of all included studies ranged from 4 to 10 out of maximal 15 points, with a mean score of 6.9. Only 23\% (n=3)\textsuperscript{7,17,30} of the included studies were considered of high quality. Most prevalent shortcomings of the studies were the following: outcome measurement not independent of prognostic factors (100\%, n=13); unstandardized or dependent measurement of prognostic factors (84.6\%, n=11and 92.3\%, n=12, respectively); no presentation of association measures and measures of variance, or no multivariate analysis performed (both 76.9\%, n=10).

Prognosis
Of all children followed for 6 to 12 months\textsuperscript{7,16,17,22-27,30,31}, 58.9±20.2\% (mean±SD) was recovered and off laxatives at the time of follow-up. Children followed for one to two years\textsuperscript{7,16,18} or for five years\textsuperscript{6,25} showed a recovery rate of 58.0±14.1\% and 56.0±11.3\%, respectively. A total of 70.8±16.8\% of the children included in a paediatric gastroenterology department (n=934) were recovered and off laxatives at time of follow-up (mean follow-up: 21.0±19.9 months)\textsuperscript{7,16,17,27,30,31}. Studies performed in general paediatric departments\textsuperscript{18,22-26} (n=647) showed a significantly lower recovery rate of 54.1±15.6\% (p<0.01)(mean follow-up: 13.0±2.5 months, p<0.01).
Studies of high methodological quality\textsuperscript{7,17,30} (n=634) showed a recovery rate of 60.6±3.2\%, compared to 61.6±20.1\% (p=0.12) in low quality studies\textsuperscript{6,16,18,22-27,31} (n=1046). In addition, six studies\textsuperscript{7,16-18,25,30} (n=992) showed that at end of follow-up, 13.9±6.6\% children recovered from constipation were still using laxatives.

**Prognostic factors**

In the present review a total of 22 prognostic factors were analysed in 61 associations with recovery. In 42 evaluations no significant association was found, in 19 evaluations a statistically significant association was reported. The mean sample size of studies that reported ‘no association’ was not significantly different from the mean sample size of studies that reported a significant association (mean sample size 140.57±104.36 versus 142.16±115.52, p=0.95). All results of the best evidence syntheses on the prognostic factors are presented in Table 3 (see Appendix).

**Demographics**

**Gender** Six studies reported on the association between gender and recovery from constipation. Two studies of high methodological quality\textsuperscript{7,30} found no statistically significant association, and one high quality study\textsuperscript{17} found that male gender was negatively associated with recovery. In addition three studies of low methodological quality\textsuperscript{6,23,24} found no significant association. In conclusion, there is conflicting evidence that gender influences recovery rate.

**Age at intake** Based on four low quality studies reporting no significant association between age and recovery, limited evidence for no association was found\textsuperscript{6,22-24}.

**Medical history**

**Age of onset/duration** One high quality\textsuperscript{30} and three low quality studies\textsuperscript{22-24} concluded that age of onset of constipation and recovery are not statistically significantly associated. In contrast, a high quality study\textsuperscript{7} showed that onset between one to four years of age is not significantly associated with recovery, but onset at the age of four years or older gives a higher recovery rate than onset before the age of one year. A low quality study\textsuperscript{6} supports the finding that an older age at onset was associated with a higher recovery rate. Based on these six papers, we conclude that evidence is conflicting.

**Family history** Two high quality studies\textsuperscript{7,30} found no significant association between a positive family history for childhood constipation and recovery. In
contrast, one low quality study\textsuperscript{5} found a negative association. Based on these three studies, we found strong evidence for no association.

Clinical symptoms

\textit{Defecation frequency at intake} Two high quality studies\textsuperscript{17,30} found no statistically significant association between defecation frequency and recovery. We found three low quality studies\textsuperscript{6,23,24} that support this finding. In conclusion, these studies provide strong evidence that there is no association between defecation frequency and recovery.

\textit{Presence of faecal incontinence at intake} Two low quality studies report on the association between the presence of faecal incontinence and recovery from constipation. One of them\textsuperscript{25} found a positive association, the other\textsuperscript{6} found no significant association. Therefore, evidence on this association is insufficient.

\textit{Frequency of faecal incontinence} We included one high quality\textsuperscript{17} and one low quality\textsuperscript{22} study that found no significant association between the frequency of episodes of faecal incontinence and recovery. In contrast, another high quality\textsuperscript{7} and low quality\textsuperscript{23} study showed that in recovered children the frequency of episodes of faecal incontinence was significantly lower at baseline than in children that did not recover during follow-up (negative association). Overall, this provides conflicting evidence.

\textit{Abdominal pain} We found three low quality studies reporting on history of abdominal pain or abdominal pain at presentation\textsuperscript{6,22,23}. All three show the same results, together providing limited evidence for no association between abdominal pain and recovery from constipation.

\textit{Urinary tract infection} Two low quality studies\textsuperscript{23,24} both found no significant association between previous urinary tract infections and recovery from constipation. Evidence on this association is insufficient.

Physical examination

\textit{Palpable rectal or abdominal mass} Two high quality studies\textsuperscript{7,17} evaluated the relation between absence of a rectal or abdominal mass on physical examination and recovery of constipation. One study\textsuperscript{7} found no statistically significant association, whereas the second study\textsuperscript{17} found absence of a palpable abdominal mass to be positively associated but absence of palpable rectal mass not significantly associated with recovery. These findings provided conflicting evidence for an association. In addition, one low quality study found no significant association between absence of an abdominal or rectal mass and recovery\textsuperscript{24}, one low quality study found a negative association\textsuperscript{23},
and one low quality study\textsuperscript{22} investigated the association between presence of an abdominal mass and treatment failure, and found a negative association.

**Additional examination**

*Balloon defecation* On the association between the ability to defecate a rectal balloon and recovery, two low quality studies\textsuperscript{22,25} report a positive association, which provides insufficient evidence. Another low quality study\textsuperscript{23} that reported on the association between the disability to defecate a rectal balloon and treatment failure, found a positive association as well.

*Relaxation of external anal sphincter* One low quality study\textsuperscript{22} found a positive association between the ability to relax the external sphincter and recovery. Another low quality study\textsuperscript{23} investigated the association between an abnormal contraction of the external sphincter and treatment failure, and also found a positive association. This provides insufficient evidence.

*Colonic Transit Time/Total Gastrointestinal Transit Time (CTT/TGTT)* We found two studies reporting on the association between CTT or TGTT and recovery. One high quality study\textsuperscript{17} found a negative association, and a low quality study\textsuperscript{6} found no significant association. In conclusion, we found limited evidence that children with a longer transit time have a lower recovery rate.

In addition, there are several prognostic factors that are investigated in one single high quality study. We found limited evidence that premature birth\textsuperscript{30}, delayed passage of meconium\textsuperscript{30} and production of large stools\textsuperscript{17} are not associated with recovery. There also is limited evidence that children with duration of symptoms of less than 3 months before presentation and children with treatment duration of less than 2 months have a higher recovery rate than children with longer treatment or symptom duration\textsuperscript{30}.

**DISCUSSION**

To our knowledge, no previous reviews on prognosis or prognostic factors of childhood constipation have been performed. In the present systematic review, only 13 papers concerning the course of childhood constipation and its determinants could be included. The majority of these studies showed poor methodological quality. Furthermore, studies were heterogeneous, encompassing different definitions, populations, outcome measures and follow-up periods. With disregard of these differences, the prognosis of constipation in children was found to be fairly good with an overall 6-12 month
recovery rate of 58.9±20.2%. Children included in a specialist setting show a higher recovery rate (70.8±16.8%) than children included in general paediatric departments (54.1±15.6%).

Based on the current literature, there is substantial evidence that defecation frequency and a positive family history are not associated with recovery of constipation. With limited level of evidence, a short duration of symptoms and treatment before presentation results in better prognosis, while studies evaluating other factors in the medical history showed no relation or were insufficient to draw firm conclusions. Conflicting evidence exists on the prognostic value of gender, age of onset and fecal incontinence. Furthermore, there is insufficient evidence available to determine the role on prognosis for one third of the prognostic factors described in literature.

Limitations

A potential shortcoming of this systematic review is the literature search. To minimize the risk of missing relevant publications as much as possible, we performed an extensive and sensitive literature search without language restrictions.

Various outcome measures have been used in the included studies. A definition of recovery, resolvement or success was described by every author except two, but no uniformity among these definitions existed. Of all symptoms that may occur with constipation, only defecation frequency was consistently included in the recovery definitions, but not all studies applied the same limiting value.

As presentation of outcome and prognostic factors varied large between the studies, it was impossible to perform a true meta-analysis on prognostic factors. Therefore we used a best evidence synthesis to be able to present a summary of these factors. We assessed methodological quality of the included studies for the best evidence synthesis using a standardized list. Due to misclassification of items, bias might occur. However, of the 13 included studies, only 3 scored a high quality. Because of low quality scores of most studies, misclassification of one item would not change the classification into a high methodological quality. Therefore we assume that the effect of a possible bias on the results is minimal.

In the best evidence synthesis, we only considered statistically significant associations as associated prognostic factors. We included several studies with a small sample size (implying low statistical power), of which misclassification could have occurred because their results did not reach statistical significance. Statistically pooling of data would have been a solution to this problem, but
was not possible because of the large clinical heterogeneity. However, we found that small sample size did not influence the results of our best evidence synthesis.

Prognosis
Despite differences between the studies included, we statistically pooled data to summarize results on prognosis of constipation. Although overall 6-12 month recovery rate of constipation in children was found to be 58.9%, a large variation (range 36.0%\textsuperscript{22} to 98.4%\textsuperscript{27}) among included studies was found. Interpretation of these pooled recovery rates is biased because studies were heterogeneous with regard to study populations and definitions of constipation and outcome measures used.

The finding that prognosis is more favourable for children in specialized centres than for children in general paediatric departments is somewhat surprising. Previous research showed that prognosis is better the earlier treatment starts after onset of constipation\textsuperscript{1}. Since children usually first present to their general practitioner or paediatrician before being referred to a more specialized centre, one would expect better prognosis in first and second line settings. Furthermore, children with constipation referred to a tertiary centre are most likely children with a more severe form of constipation unresponsive to conventional treatment. On the other hand, children seen in specialist settings may receive more advanced or more aggressive treatment than children in general paediatric settings. Because of the large diversity between the studies, it was impossible to make a valid comparison in study population or treatment regimens applied.

Prognostic factors
Current literature shows strong evidence that a positive family history is not associated with recovery of constipation. Strong evidence also exists that defecation frequency is not of influence on prognosis of constipation. This finding supports the idea that functional constipation is a disease entity which comprises more aspects than defecation frequency only, as is described recently in the Rome III criteria\textsuperscript{4}.

The present review does not provide insight on the prognostic value of fecal incontinence. A negative influence would be expected based on experience, but at the moment evidence is conflicting due to a lack of studies evaluating its role.
Future research

The results of our review show that further research by means of large follow-up studies on prognosis of childhood constipation and factors of influence on prognosis is necessary. We recommend using a clear definition for both the diagnosis of constipation as for recovery of constipation. This definition preferably is a worldwide used uniform definition, taking into account all aspects of constipation, such as the recently developed Rome III criteria. It is important to investigate prognosis not only in children seen in specialized settings, but also in a more general population to gain insight in possible differences between these settings. In addition, more detailed registration of symptom severity and treatment regimens applied is needed.

CONCLUSION

The few studies published on prognosis of childhood functional constipation and its predictive factors showed large clinical diversity and poor methodological quality. Overall 6 to 12 month recovery rate of constipation in children was found to be 58.9%, but large variation ranging from 36.0% to 98.4% among the included studies was found. Children included in a specialist setting show a higher recovery rate than children included in general paediatric departments. Recovery rate showed no relation with defecation frequency or positive family history. Based on the current literature, we are not able to identify a group of children at risk for poor outcome.
REFERENCES


Chapter 5

Long term prognosis of childhood constipation: clinical outcome in adulthood

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Submitted


**ABSTRACT**

**Background & Aims**
Long term follow-up studies in children with functional constipation are scarce, but results suggest that symptoms may persist for many years. Knowledge about the outcome at adult age is lacking. In this study we examine the long-term prognosis of constipated children when they reach adult age and identify prognostic factors associated with poor and good clinical outcome.

**Methods**
In a tertiary hospital in the Netherlands, children (5-18 years) diagnosed with functional constipation were eligible for inclusion. After an initial 6-week treatment protocol, prospective follow-up was conducted at 6 and 12 months and annually thereafter, using a standardized questionnaire. Good clinical outcome was defined as ≥3 bowel movements per week for at least 4 weeks with <2 fecal incontinence episode per month, irrespective of laxative use.

**Results**
A total of 401 children (260 male, median age at study entry 8 years [25th-75th percentiles 6-9]), were included and a median follow-up duration of 11 years (9-13) was accomplished. Drop-out rate during follow-up was 15%. Good clinical outcome was achieved by 80% of patients at the age of 16 years and thereafter this percentage remained constant at around 75%. The following clinical characteristics were associated with poor clinical outcome at adult age: older age of onset (OR 1.15, 95%CI 1.02-1.30, p=0.04), longer delay between age of onset and first visit to our outpatient clinic (OR 1.24, 95%CI 1.10-1.40, p=0.001), and a lower defecation frequency at study entry (OR 0.92, 95%CI 0.84-1.00, p=0.03).

**Conclusions**
A quarter of children with functional constipation continued to have symptoms at adult age. Certain risk factors for poor clinical outcome in adulthood were identified. Referral to a specialized clinic should be considered at an early stage for children unresponsive to first line treatment.
INTRODUCTION

Constipation is a common disorder in children, accounting for around 3% of visits to pediatric clinics and even 10-25% to pediatric gastroenterology clinics. As no organic cause is found in approximately 90% of children, these children are diagnosed with functional constipation. The general belief that functional constipation is self-limiting and that children grow out of their symptoms, is not supported by several long-term follow-up studies. Persistence of symptoms is reported in 30 to 52% of children with functional constipation in studies with at least five years of follow-up. Children with chronic symptoms of functional constipation suffer from lower quality of life, as found by children's self-report and parent proxy measurement. Still, larger prospective studies are needed to determine the outcome of childhood constipation. Follow-up of a large cohort of children with constipation in our pediatric gastrointestinal clinic showed that symptoms persisted in one third of children at the age of 16 years and beyond. However, results were imprecise as only a quarter of the included children reached 16 years of age in that study. To date, scarce data exists on the prognosis of childhood constipation when they reach adult age. A small retrospective study found that the frequency of constipation in 20 adults with a history of childhood constipation was not different from that of 17 controls (25% versus 23.5%). However, in the same study, childhood constipation appeared to be a predictor of irritable bowel syndrome (IBS) in adulthood. With longer follow-up of our cohort now available, our aim was to evaluate whether our previous findings about the long-term outcome of children with constipation would sustain. Furthermore, we wanted to determine which clinical characteristics at time of first presentation to the pediatric gastrointestinal outpatient clinic were associated with persistence of constipation in adulthood.

METHODS

Patients

All patients who participated in one of the clinical studies on childhood constipation between 1991 and 1999 were eligible for inclusion. In these studies, functional constipation was defined as presence of at least 2 of the following 4 criteria: defecation frequency less than three times per week; two or more episodes of fecal incontinence per week; passage of very large amounts of stool at least once every 7 to 30 days; a palpable abdominal or rectal mass on physical examination. In addition, only patients with a minimum
age of 5 years who had received laxative treatment for at least 2 months before their initial presentation were included. Excluded were children with organic causes of constipation (such as Hirschsprung’s disease, spina bifida (occulta), hypothyroidism or other metabolic or renal abnormalities), mental retardation and children using drugs influencing gastrointestinal function other than laxatives.

Follow-up and data collection
After the last visit of the initially intensive 6-8 week treatment protocol, follow-up was carried out for each patient at 6 months and annually until 2005. Between 2005 and 2007 every patient still in the cohort was contacted once more. Follow-up was conducted during an outpatient-clinic visit or by telephone when the child had been discharged from the outpatient clinic. If contact by phone failed, an explanatory letter was mailed to the patient’s current address. This letter contained study information, an invitation to contact the pediatric gastrointestinal department for follow-up and a non-response form. This non-response form could be returned in a prestamped and addressed envelope. Subjects who indicated at any point during follow-up that they no longer wished to participate in this follow-up cohort were contacted no further. If the address proved wrong, the investigators tried to obtain new contact details by contacting the patient’s last known general practitioner or though municipal archives they were lastly registered.

During each follow-up interview, a standardized questionnaire was used to obtain information regarding current clinical outcome. Data concerning defecation frequency, stool consistency and size, painful defecation, fecal incontinence frequency, abdominal pain and laxative use were based on a six-week period before the moment of follow-up. In addition to this 6-week period all relapses between the previous and current follow-up time were documented.

Definition of clinical outcome
Good clinical outcome during follow-up was defined as a defecation frequency of ≥3 per week for a period of ≥4 weeks with less than 2 episodes of fecal incontinence per month, while not receiving laxatives in the previous 4 weeks (category 1). For more detailed assessment of clinical outcome, three additional categories were defined: the second category of children had good clinical outcome, while still using laxatives (category 2), whereas the two other groups had poor clinical outcome, either without the use of laxatives (category 3) or with the use of laxatives (category 4). A child was considered to have had a
relapse, when the defecation frequency decreased to less than 3 times per week and/or fecal incontinence frequency increased to more than once per fortnight after initial good clinical outcome.

Statistical analysis
Baseline characteristics of the cohort are reported in a descriptive way. Comparison between patients with complete follow-up and those who dropped out was conducted with Mann Whitney-U-tests for continuous outcomes and Chi-square tests for dichotomous outcomes. For each of the fixed time points of follow-up, the distribution of patients over the four defined categories of clinical outcome was computed. The frequency and timing of first good clinical outcome were presented in a Kaplan Meier-curve. Furthermore, a similar Kaplan-Meier curve was computed for relapse after patients had had their first good clinical outcome. Generalized estimation equation (GEE) models were used to gain insight into the association between clinical characteristics and clinical outcome at adult age. GEE models are an extension of generalized linear models in order to deal with correlated outcomes. Within the GEE framework, a working correlation matrix is estimated to adjust the standard errors for the correlation that is present. No mathematical pattern was imposed on the covariance structure for measurements within the same individual (unstructured). In the GEE analysis, the four clinical outcome categories were reduced to a binary outcome: good clinical outcome (categories 1 and 2) versus poor clinical outcome (categories 3 and 4). To take into account the possible fluctuation of constipation symptoms from year to year, adult age was defined as the window from age 16 up to 18 years. Thus, all observations available per patient in this age range were included. A limited set of predefined baseline factors was entered into the model without any further selection strategy. These candidate factors were selected based upon previous research findings and our own interest. The following factors were examined: gender, age of onset of constipation, delay (i.e. time between age of onset and first presentation to our pediatric gastrointestinal outpatient clinic), defecation frequency and fecal incontinence frequency at first presentation to the outpatient clinic. Both univariate and multivariate GEE models were run and results were expressed as together with 95% confidence intervals and corresponding Chi-square tests. In addition, the frequency and timing of relapses in patients with good clinical outcome at adult age were presented in a Kaplan Meier curve.
Statistical analyses were performed by using SPSS windows version 12.0.2 (SPSS Inc., Chicago, Illinois, USA) and SAS version 9.1 (SAS Institute Inc., Cary, North Carolina, USA). Statistical significance was accepted at p < 0.05.

RESULTS

Baseline characteristics and completeness of follow-up

Between 1991 and 1999, a total of 416 patients with functional constipation were included in the two clinical studies. Of this cohort, 15 children were excluded for follow-up due to incorrect inclusion in the research protocols (n=15). Thus, a total of 401 children with functional constipation (65% males, median age (25th-75th percentiles) at entry 8 (6-9) years) were included in the present study. Median duration of follow-up was 11 (9-13) years. Baseline characteristics are given in table 1.

<table>
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<tr>
<th>Table 1. Baseline characteristics (n=401)</th>
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<td>Rectal scybalus, %</td>
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<td>Positive family history, %</td>
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During this follow-up study, there was a drop-out rate of 15% (n=62). Lost to follow-up occurred for the following reasons: (1) no contact information could be retrieved n= 14; (2) no response to a written invitation to contact the pediatric gastrointestinal department for follow-up n= 33; (3) decline of further participation n= 7; (4) died in a car accident n=1; (5) other reasons n= 7. Of the remaining 339 patients (85%), 244 patients (72%) reached the age of 18 years. The drop-outs differed from the followed up patients with respect to age at first visit to the outpatient clinic: median age (25th-75th percentiles) 7 (6-9) versus 8 (7-10), p=0.01. No other differences in baseline characteristics were found (data not shown).

Figure 1. Clinical outcome of patients per follow-up year, divided over the 4 defined outcome categories: category 1= good clinical outcome without laxative use; category 2= good clinical outcome with laxative use; category 3= poor clinical outcome without laxative use; category 4= poor clinical outcome with laxative use. The number on the upper row above each bar shows the number of patients due for follow-up that year. Numbers of the second row show the patients reached for follow-up that year.

Clinical outcome during follow-up

The distribution of patients over the four defined clinical outcome categories per follow-up year is shown in figure 1. After one year, 50% of children achieved good clinical outcome with 11% of these children still using laxatives. Thereafter, a gradual increase in the proportion of patients with clinical success was seen: 64% at 5 year follow-up to 81% at 10 year follow-up. By that time, only 4% of patients were still treated with laxatives, of which 3% achieved good clinical outcome compared to 1% with poor clinical outcome. After 10 years, the overall success percentage was more or less stable around 80%.

Clinical outcome according to biological age is depicted in figure 2. During childhood a steady increase in good clinical outcome is found, from 50% at the age of 5 years to 80% at the age of 16 years. Thereafter, success percentages
at adult age remained constant around approximately 75%. Laxative use at the age of 18 years was limited to 10 patients with good and 1 patient with poor clinical outcome.

**First clinical success and relapse after initial success**

Figure 3 shows the cumulative percentage of children achieving at least one period of good clinical outcome during follow-up. Girls achieved their first good clinical outcome significantly faster and more frequently than boys \(p<0.001\). After half a year, 55% of girls achieved initial clinical success compared to 33% of boys. At two years in follow-up, 42% of boys had still not achieved good clinical outcome, while this applied to 30% of girls. This gender difference disappeared with longer follow-up: after 10 years 94% of girls and 92% of boys had achieved at least one period of good clinical outcome.

The frequency and timing of relapses after initial success are depicted in figure 4. Relapses occurred in 13% of girls and 25% of boys within one year after achievement of good clinical outcome. With time, a steady increase in patients with a relapse was seen, resulting in an overall relapse percentage of 46% in the 10 year period after initial success. No significant difference in relapse percentages between boys and girls was found \(p=0.52\).
Prognostic factors for persistence of constipation at adult age

A total of 333 patients achieved the age of 16 years. Of these patients, 302 (63% males) were reached for follow-up. All 816 follow-up evaluations of these patients between 16 and 18 years of age were included in the GEE model for analysis. Univariate analysis showed a significant association between delay and clinical outcome, indicating that patients who had a longer period between onset of symptoms and their first visit to our pediatric gastrointestinal outpatient clinic had more periods with poor clinical outcome (OR 1.12, 95%CI 1.03-1.22, p=0.02). No correlation between other baseline characteristics (age of onset, gender, defecation frequency and fecal incontinence frequency at intake) and clinical outcome was found.

In the multivariate analysis, clinical outcome was found to be significant correlated to three baseline characteristics: delay (OR 1.24, 95%CI 1.10-1.40, p=0.001), age of onset (OR 1.15, 95%CI 1.02-1.30, p=0.04) and defecation frequency (OR 0.92, 95%CI 0.84-1.00, p=0.03). Gender and fecal incontinence...
frequency were not correlated to clinical outcome. To better illustrate the absolute impact of these findings, we introduce the following patient groups. A typical patient from our study is a male patient who had his onset of symptoms at the age of 3 years and presented for the first time at our outpatient clinic with a delay of 5 years, reporting a defecation frequency of twice a week and 10 episodes of fecal incontinence per week. The estimated risk for poor clinical outcome in this patient would be 16%. In such a patient, if delay between age of onset and first visit to our outpatient clinic would have been one year, the estimated risk for poor clinical outcome at adult age (16-18 yrs) would decrease to 7%. If his delay instead of one year would have been nine years, his estimated risk would increase to 31%. The influence of age of onset of constipation can also be illustrated using our typical patient by varying the age of onset. The estimated risk of poor clinical outcome at adult age is around 11% in such a patient if complaints of constipation started at birth compared to 24% in a patient with onset of complaints at age 7. Finally, a low defecation frequency at first presentation, i.e. once per week, corresponded with 17% estimated risk of poor clinical outcome at adult age, and this risk decreased to 11% for patients presenting with defecation frequency of 7 times per week.

Relapses during adult age

After achievement of good clinical outcome at adult age, relapses occurred significantly more frequent in females than in males (figure 5). Within one year after clinical success, relapse rate was similar for females and males, 5% and 4% respectively. Thereafter, cumulative relapse frequency increased to 28%.

Figure 5. The cumulative percentage of patients who relapsed after good clinical outcome at adult age, showing a significant greater percentage of relapse in females than in males (p=0.01).
after 5 years and 40% after 7 years in females compared to 12% and 20% in males (p=0.01).

**DISCUSSION**

Our long-term follow-up study reveals that in approximately 25% of children with functional constipation, symptoms persisted into adulthood. Although girls achieved their first clinical success faster and more frequently than boys, this difference disappeared after 10 years follow-up with a cumulative initial success percentage of 94% for girls and 92% for boys. Relapses after initial success occurred in approximately half of the children within 10 year follow-up, showing no difference between boys and girls. Poor clinical outcome at adult age was associated with a later age of onset, longer delay between age of onset and first presentation to our pediatric gastrointestinal outpatient clinic, and lower defecation frequency at first presentation. Lastly, relapses at adult age were more common among females than males.

In line with our earlier observations 12, good clinical outcome in this study population showed a steady increase with longer duration of follow-up. As shown in figure 1, laxative use among the subgroup of children with poor clinical outcome is limited. As soon as at 6 months follow-up, two-third of children with poor clinical outcome no longer used laxatives and at 10 years follow-up only 4% of these children was still on laxatives. This limited use of laxatives is most likely explained by the fact that these patients are tired of taking laxatives for long periods without any result. Furthermore, many parents are anxious giving their children laxatives for longer period of time. However to date, there is no strong evidence that long-lasting laxative use leads to tolerance or causes mucosal or neurological colonic damage 19.

On the other hand, our follow-up results seem to indicate that part of the children with poor clinical outcome achieved success over the years without the use of laxatives. Clinical outcome according to follow-up duration seem to be related to outcome according to biological age, as success percentages showed a similar steady increase with biological age. In line with the long-term follow-up findings in children with functional non-retentive fecal incontinence from our group, a steady increase in achievement of good outcome during puberty was seen 20. One can hypothesize that during puberty the young adolescent learns to take more responsibilities for its own actions in general. In relation to their defecation problems, they may in particularly take better responsibility for regular toileting and no longer withholding their urge to defecate. Peer-pressure and social embarrassment may contribute to this.
Yet, the fact that a quarter of children with functional constipation reported persisting symptoms into young adulthood refutes the general belief that all children grow out of it over the years. In this respect, extension of follow-up in our cohort confirms our previously reported clinical results 12. To date, comparison to other follow-up studies is still hampered by differences in applied definitions of constipation 6, 8, 15, 21, small numbers of patients 7-9, 15, 22, 23, low follow-up percentages 6-9, 21, 22 or due to retrospective or cross-sectional study designs instead of longitudinal ones 15, 21, 24.

Poor clinical outcome at adult age was correlated with three clinical characteristics: age of onset, delay between onset of symptoms and the first visit to our outpatient clinic and defecation frequency at baseline. Firstly, later age of onset was found to be related to poor clinical outcome. This seems in contrast to previous findings in this cohort, reporting that onset before the age of one year resulted in lower success rate compared to onset at the age of four years or older 12. It could be that different factors are predictive for clinical outcome at adult age than at childhood. One could hypothesize that the onset of constipation at older age, for instance onset during adolescence, is an early expression in the continuum of functional gastrointestinal disorders such as adult constipation or constipation-predominant irritable bowel syndrome (IBS). In a small retrospective study by Kahn et al, childhood constipation appeared to be a predictor of IBS in adulthood 15. Furthermore, our study showed that relapses at adult age occurred more often in females than males. Although we can not fully explain this finding, it seems in line with several adults studies reporting a higher predominance of functional gastrointestinal disorders, such as IBS, in females than males 25-28. Whether female patients in our cohort experienced a true relapse of their childhood constipation or developed a new functional gastrointestinal disorders like constipation-predominant IBS needs to be further studied.

Secondly, longer delay between age of onset and first visit to our outpatient clinic was associated with poor clinical outcome at adult age. We find it hard to understand why this is. On the one hand, we hypothesize that the earlier children are referred to an outpatient clinic experienced in treating children with constipation, the sooner they receive the adequate and intensive treatment necessary. A previous study in infants with constipation showed that infants with duration of symptoms less than 3 months before presentation achieved higher success rates than those with longer symptom duration 29. Yet, in contrast to a relatively short delay in the study by van den Berg et al., the median delay in our patient cohort was 5 years, indicating that other factors may have biased the group of children with longer delay. One could hypothesize that the role of parents in managing their child’s defecation problem could be an potential
delaying factor, as well as contribute to poor clinical outcome. A subgroup of parents may have waited longer to visit a doctor for treatment as they initially perceived this defecation problem being of transient nature. Furthermore, inadequate parental style with respect to setting limits to the child in general and specifically regarding toileting behaviors is thought to play an important role in both development and persistence of constipation 30. Subsequently, parental inability to set limits may also complicate adequate treatment. Nevertheless, further studies are needed to support these presumptions.

Lastly, a low defecation frequency was associated with poor clinical outcome. This is in contrast to several studies that found no association between defecation frequency and clinical outcome 7, 8, 29, 31, 32. Yet, in children with intractable constipation a low defecation frequency could reflect a primary colonic dysmotility due to neuromuscular abnormalities or result from an acquired motility disorder after years of severe functional constipation 33-39.

Some limitations of this study need to be addressed. Our population consisted of children referred to a tertiary care centre for treatment of chronic constipation. Therefore, our results cannot directly be generalized to children seen in primary care centers or general pediatric settings. Furthermore, to determine clinical outcome at adult age we still used our pediatric definition of constipation. In future follow-up studies of our patient cohort, it would be interesting to determine clinical outcome at adult age by using the definition of functional constipation for adults as well as those of other functional gastrointestinal disorders to find out whether childhood constipation is an early expression in the continuum of functional gastrointestinal disorders.

In conclusion, a quarter of children with functional constipation continued to have symptoms at adult age. Older age of onset, longer delay between onset of symptoms and referral to a specialized pediatric gastrointestinal clinic and lower defecation frequency at intake were related to poor clinical outcome at adult age. Referral to a specialized clinic should be considered at an early stage for children unresponsive to first line treatment.
REFERENCES


Part III

Health-related quality of life and chronic constipation
Chapter 6

Health related quality of life in children with constipation-associated fecal incontinence

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Submitted
ABSTRACT

Objectives
Childhood constipation is associated with lower health-related quality of life (HRQoL) assessed with generic questionnaires. Using a disease specific questionnaire, this study aimed to evaluate HRQoL in children with constipation in association with clinical characteristics.

Study design
Hundred-fourteen children with constipation-associated fecal incontinence, 8-18 years, filled out the Defecation Disorder List at a Dutch tertiary hospital. Correlations and linear regression analysis between clinical characteristics and scores on emotional and social functioning were calculated. Specific concerns of children were described by individual item scores of these scales.

Results
Higher frequency of fecal incontinence episodes was associated with lower emotional and social functioning (Spearman's rho -0.32, p=0.001 and -0.28, p=0.002, respectively). Linear regression analysis showed a significant association between social functioning and fecal incontinence (beta=-0.30; p=0.002). Between 70-80% of children were concerned about experiencing fecal incontinence unnoticeably and other people smelling them. Children did not report having fewer friends and participated well in social events. In contrast, self-reported prevalence of bullying by other children was high (23%).

Conclusion
Lower HRQoL regarding disease specific emotional and social functioning was reported in children with frequent episodes of constipation-associated fecal incontinence. The majority of children reported relatively more emotional concerns than social consequences.
INTRODUCTION

Childhood constipation is worldwide one of the most common pediatric gastrointestinal disorders with prevalence in the general population ranging from 0.7% to 29.6% \(^1\). Functional constipation is characterized by a low defecation frequency, passage of hard and large stools and painful defecation without an underlying organic cause \(^2\). Up to 84% of children with constipation experience frequent episodes of fecal incontinence, which is thought to be overflow diarrhea secondary to fecal impaction \(^3\).

Functional constipation and secondary fecal incontinence are a source of distress and concern for the child and its family. Symptoms often persist for years and relapses are common \(^3-6\). Furthermore, fecal incontinence may cause feelings of guilt and embarrassment and is associated with behavior problems, both internalizing, e.g. social withdrawal, anxiety and depression, and externalizing, e.g. delinquent behavior and aggression \(^7-9\). Successful treatment is often associated with improvement of behavior \(^10-12\). Nonetheless, it remains the question whether behavior problems are the result of fecal incontinence or vice versa.

Over the past years, impact of chronic diseases on children is increasingly assessed by measuring health related quality of life (HRQoL). HRQoL refers to the specific impact of an illness on physical, social and emotional functioning \(^13\). In a recent study, parents reported lower HRQoL regarding both physical and psychosocial functioning, and general health and behavior aspects in their children with functional defecation disorders compared to healthy children \(^14\). Both self report and parental assessment showed that long duration of symptoms and physical complaints associated with constipation may result in impaired HRQoL in children with constipation \(^15\). HRQoL in these studies was measured by a generic questionnaire and thus may lack precision and sensitivity to identify important effects of distinctive symptoms of functional constipation, such as fecal incontinence. Recently, a disease-specific questionnaire, the Defecation Disorder List (DDL), was developed to assess the impact of functional constipation and fecal incontinence on HRQoL in children \(^16\). Using this questionnaire, we aimed to describe HRQoL in children with constipation with fecal incontinence and to investigate to what extent clinical characteristics are associated with reported HRQoL.
METHODS

Patients and Procedure

All consecutive patients between 8-18 years of age referred by general practitioners (GP) and pediatricians to the gastrointestinal outpatient clinic at the Emma Children’s Hospital between September 2001 and November 2005 were eligible. Children fulfilled the definition of pediatric functional constipation, comprising the presence of at least two of the following four symptoms: 1) spontaneous defecation frequency <3 per week, 2) fecal incontinence episodes ≥2 per week, 3) passage of large diameter stools that may obstruct the toilet and 4) palpable abdominal or rectal mass on physical examination 17. Children with organic causes of constipation, including Hirschsprung’s disease, muscle disorders, prior recto-anal surgery, spina bifida, mental retardation or hypothyroidism were not eligible. The study protocol was approved by the medical ethical committee of the Academic Medical Center of Amsterdam. All children and/or parents gave informed consent.

For assessment of clinical symptoms of functional constipation, children and their parents were asked to record defecation frequency and fecal incontinence episodes, together with passage of large amounts of stools, presence of painful defecation, abdominal pain and urinary incontinence in a diary one week prior to their first visit to the outpatient clinic. During this week laxative treatment was discontinued. At the first visit, a standardized interview was conducted to determine defecation pattern including defecation frequency, stool consistency, painful defecation, passage of large amount of stools, fecal incontinence episodes, abdominal pain and urinary incontinence. Furthermore, information was collected regarding age of onset of symptoms, treatment history and family history of gastrointestinal disorders. Abdominal and rectal examination was performed to evaluate the presence of fecal impaction.

The DDL was handed out to all children at the second visit to the outpatient clinic. This second visit was scheduled one week (maximal range to two weeks) after the first visit. Three days in advance of this second visit, disimpaction with rectal enemas or bisacodyl suppositories once daily was prescribed, in order to achieve complete disimpaction in all children. At the start of the second visit, the interviewer explained the questionnaire and stayed in the room. Children were asked to fill out the DDL by themselves without discussion with their parents. Maintenance treatment in the form of oral laxatives was started after this second visit.
Instrument

The DDL has been developed to assess the impact of functional defecation disorders in children between 7 and 15 years in a study with 27 children. Tested in children with constipation and functional non-retentive fecal incontinence, it was found to be a valid and reliable instrument. The questionnaire consists of 37 items encompassing four domains: 1. constipation related (3 items); 2. emotional functioning (13 items); 3. social functioning (11 items); 4. treatment/intervention (10 items). Items are phrased as statements in the first person and in the present tense, except for four items addressing feelings or symptoms in the past two weeks. Children were asked to indicate whether they agree with a statement on a five-point Likert scale. Depending on the kind of question, the following answering options were used: “very much – much – quite a lot – a little – not at all” or “always – often –sometimes – rarely – never”. For calculation of domain scores, items were reverse scored so that higher scores indicate a better HRQoL. In the calculation of the domain scores a maximum of 30% of missing items per domain was allowed for. These missing values were then replaced by the mean value of the non-missing item scores. Considering the fact that previously found reliabilities for the domains constipation related and treatment/intervention (Cronbach’s alpha 0.65 and 0.61, respectively) could not be replicated in this study (Cronbach’s alpha 0.35 and 0.53, respectively), the sum scores of these domains were left out for further analysis. Reliabilities for the domains emotional and social functioning (Cronbach’s alpha’s 0.72 and 0.65, respectively) corresponded with previously found reliabilities (Cronbach’s alpha 0.76 and 0.63, respectively). Ranges of sum scores were 13 to 65 for domain emotional functioning and 11 to 55 for domain social functioning.

Statistical analysis

Statistical analysis was performed by using SPSS windows version 12.0.2 (SPSS Inc., Chicago, Illinois, USA). Clinical symptoms of functional constipation at baseline are presented in a descriptive way. Differences between children included or excluded for analysis were tested for significance by Mann-Whitney U test for continuous data or Chi-square test for categorical data. Correlations between sum scores of the domains emotional and social functioning, and clinical characteristics (gender, age at intake, durations of symptoms, defecation frequency per week and fecal incontinence frequency per week) were calculated by Pearson correlation or Spearman’s rho. Linear regression analysis was performed with the above mentioned characteristics included in the model. For both regressions, the explained variance (adjusted R square) was determined, and it was tested using the F-test. T-values and
their significance level were calculated to test the hypothesis whether the contribution (the regression coefficient ($\beta$)) of an entered variable significantly differed from zero. Furthermore, individual item scores of domains emotional and social functioning are presented.

**RESULTS**

**Patient characteristics**

A total of 136 children with constipation participated in the study. For unknown reasons the DDL could not be retrieved in the medical notes in three children, who were therefore excluded from the study. As the DDL aims to measure the consequences of constipation and fecal incontinence, children with no fecal incontinence at baseline and/or no answers to specific questions on fecal incontinence (8 items of the in total 37 DDL-items) were excluded for analysis. Based on this criterion, the DDL of nineteen children were excluded. In total, the DDL of 114 patients with constipation-associated fecal incontinence could be included for analysis.

| Table 1. Baseline characteristics of 114 children with constipation and fecal incontinence |
| Demographics |
| Age at intake, mean (SD), y | 10.8 (2.0) |
| Age group at intake, No (%) |
| 8-12 y | 88/114 (77.2) |
| ≥12 y | 26/114 (22.8) |
| Boys, No (%) | 78/114 (68.4) |
| History |
| Duration of symptoms, mean (SD), y | 6.7 (2.5) |
| Period of treatment, median (IQR), mo | 18.0 (6.0-48.0) |
| Positive family history, No (%) | 43/111 (38.7) |
| Clinical symptoms |
| Defecation frequency/week, median (IQR), < 3 times per week, No (%) | 2.0 (1.0-3.0) |
| ≥7 times per week, No (%) | 82 (71.9) |
| Fecal incontinence frequency/week, median (IQR) |
| < 3 times per week, No (%) | 8.4 (3.5-14.0) |
| ≥7 times per week, No (%) | 67 (58.8) |
| Large amount of stool, No (%) | 82/113 (72.6) |
| Painful defecation, No (%) | 62/110 (56.4) |
| Abdominal pain, No (%) | 81/113 (71.7) |
| Urinary incontinence, No (%) | 27/114 (23.7) |
| Physical examination |
| Abdominal scybalus, No (%) | 28/102 (27.5) |
| Rectal scybalus, No (%) | 53/109 (48.6) |

Abbreviations: y: year; SD: Standard Deviation; IQR: Inter quartile range
Baseline characteristics of these 114 children are given in table 1. The majority of children (77.2%) were between 8-12 years of age at intake. Mean duration of symptoms was 6.7±2.5 years, with a median period of treatment before intake of 18.0 months (range 0-132 months). Prior to enrollment, 13% of children had only been seen by their general practitioner (GP), 45% visited both their GP and a general paediatrician, 41% visited not only their GP and/or a paediatrician, but also a psychologist and/or a physiotherapist. Eighty percent of all children, with varying duration, had received oral laxatives (lactulose or polyethylene glycol) at some point in the 18 months prior to enrolment. Rectal enemas were no part of maintenance therapy in this group of patients, and given sporadic in less than 10% of children as disimpaction therapy. In addition, recommendations to introduce a fibre rich diet were made in 10% of children, in 30% advice to start with toilet training and a reward system was given, 50% received recommendations about both a fibre rich diet and toilet training/reward system, and in 10% of children no advice on dietary changes or behavioral strategies was given. Adherence to oral laxative treatment and these recommendations might have varied and could not be determined retrospectively.

At intake, a defecation frequency of less than three times per week was found in 71.9% of all children and 58.8% experienced seven or more episodes of fecal incontinence per week. The group of patients excluded from analysis consisted of significantly less boys compared to the group of children included for analysis (45.5% versus 68.4%, p= 0.04). No other differences in baseline characteristics were found between these two groups (values not given).

DDL domain sum scores

The missing value count was 1.0% for domain emotional functioning and 0.3% for domain social functioning. Mean sum score was 43.1±7.4 for domain emotional functioning (range 22-57; mean item score 3.3) and 39.2±6.1 for domain social functioning (range 23-51; mean item score 3.6). The association of clinical characteristics on domain sum scores is shown in table 2. The presence of more episodes of fecal incontinence was significantly related to lower emotional and social functioning (correlation: -0.32; p=0.001 and -0.28; p=0.002, respectively). Other factors had no association with domain sum scores. Social functioning could be significantly explained by the clinical characteristics; gender, age at intake, duration of symptoms, defecation frequency and fecal incontinence frequency per week (F= 2.99, df= 5, p= 0.01; adjusted $R^2 = 0.08$). Of these clinical characteristics, only fecal incontinence was significantly related to social functioning ($\beta$-value -0.30; p=0.002).
### Table 3. Children's reported concerns about fecal incontinence and constipation (n = 114)

<table>
<thead>
<tr>
<th>No. Questions</th>
<th>n</th>
<th>Answers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional functioning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. I am worried about not being able to defecate</td>
<td>114</td>
<td>7.0</td>
</tr>
<tr>
<td>2. I think defecation will become worse in the future</td>
<td>112</td>
<td>0.9</td>
</tr>
<tr>
<td>3. I feel exactly when I need to go to the toilet to defecate</td>
<td>114</td>
<td>10.5</td>
</tr>
<tr>
<td>4. I am afraid of having feces in my underwear</td>
<td>112</td>
<td>10.7</td>
</tr>
<tr>
<td>5. I am worried about having feces in my underwear unnoticeably</td>
<td>113</td>
<td>8.8</td>
</tr>
<tr>
<td>6. I think it is unfair to have these defecation problems</td>
<td>114</td>
<td>9.6</td>
</tr>
<tr>
<td>7. I have been angry to have this problem in the past two weeks</td>
<td>111</td>
<td>4.4</td>
</tr>
<tr>
<td>8. I think having feces in my underwear is awful</td>
<td>114</td>
<td>36.0</td>
</tr>
<tr>
<td>9. I am ashamed for feces in my underwear</td>
<td>114</td>
<td>15.8</td>
</tr>
<tr>
<td>10. I do not like having to stay on the toilet for a long time</td>
<td>112</td>
<td>13.4</td>
</tr>
<tr>
<td>11. I am happy with my life</td>
<td>113</td>
<td>41.7</td>
</tr>
<tr>
<td>12. My defecation problem has influence my family</td>
<td>111</td>
<td>9.9</td>
</tr>
<tr>
<td>13. I think I am able to solve my defecation problems by myself</td>
<td>113</td>
<td>8.8</td>
</tr>
<tr>
<td>Social functioning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. I am worried that other people will smell feces in my underwear</td>
<td>113</td>
<td>31.0</td>
</tr>
<tr>
<td>2. Other children bully me because of having feces in my underwear</td>
<td>114</td>
<td>2.6</td>
</tr>
<tr>
<td>3. I am worried about having feces in my underwear at school</td>
<td>114</td>
<td>12.3</td>
</tr>
<tr>
<td>4. I have been missing hobbies/ school camp/ parties because of my defecation disorder in the past two weeks</td>
<td>114</td>
<td>0</td>
</tr>
<tr>
<td>5. I do not like going to the toilet somewhere else</td>
<td>114</td>
<td>2.6</td>
</tr>
<tr>
<td>6. I think that the toilet at school is unclean</td>
<td>114</td>
<td>30.7</td>
</tr>
<tr>
<td>7. I think feces in my underwear is dirty</td>
<td>114</td>
<td>43.9</td>
</tr>
<tr>
<td>8. My defecation problems causes problems when going on holiday/ school camp</td>
<td>113</td>
<td>15.9</td>
</tr>
<tr>
<td>9. I felt terrible the past two weeks</td>
<td>113</td>
<td>2.7</td>
</tr>
<tr>
<td>10. Because of feces in my underwear I have fewer friends</td>
<td>113</td>
<td>1.8</td>
</tr>
<tr>
<td>11. I try to hide my defecation disorder</td>
<td>114</td>
<td>18.4</td>
</tr>
</tbody>
</table>

### Table 2. Association between clinical characteristics and emotional and social functioning scales

<table>
<thead>
<tr>
<th>Emotion and Social functioning scales</th>
<th>Emotional functioning</th>
<th>Correlation*</th>
<th>P-value</th>
<th>β-value**</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td>-0.05</td>
<td>0.63</td>
<td>-0.03</td>
<td>0.79</td>
</tr>
<tr>
<td>Age at intake</td>
<td></td>
<td>0.009</td>
<td>0.92</td>
<td>-0.002</td>
<td>0.99</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td></td>
<td>0.05</td>
<td>0.60</td>
<td>-0.01</td>
<td>0.92</td>
</tr>
<tr>
<td>Defecation frequency/ week</td>
<td></td>
<td>0.02</td>
<td>0.83</td>
<td>-0.05</td>
<td>0.61</td>
</tr>
<tr>
<td>Fecal incontinence frequency/ week</td>
<td></td>
<td>-0.32</td>
<td>0.001</td>
<td>-0.28</td>
<td>0.006</td>
</tr>
</tbody>
</table>

* Pearson correlation for normally distributed data or Spearman's rho for not normally distributed data, Regression analysis: ** F= 1.64, df = 5, p = 0.16; adjusted R2 = 0.03; ***F= 2.99, df= 5, p= 0.01; adjusted R2 = 0.08
Specific concerns

The individual item scores of the scales emotional functioning and social functioning are shown in table 3; online. For description we clustered these individual scores into two categories: always, often and sometimes versus rarely and never or very much, much and quite a lot versus a little bit and not at all.

Scores on emotional functioning showed that two-third of the children was afraid of having feces in their underwear and 70% were afraid that this happened unnoticeably. A total of 78% of the children found it awful to have feces in their underwear, while being ashamed for their fecal incontinence was reported in half of the children. In the weeks prior to filling out the DDL, 37% percent of the children had been angry about having a defecation problem. Less than 40% of the children thought they are able to solve their defecation problem by themselves, but 80% thought that this problem will not become worse in the future. Almost two-third of the children stated that their defecation problem did not influence their family. In general, the vast majority of children were happy with their life.

The social functioning scale showed that 80% of the children...
were worried that other people will smell them when having fecal incontinence. Around two-third of the children was worried that fecal incontinence happens during school time. Approximately 40% tries to hide their defecation disorder. Almost 90% of the children agreed with the statement that having feces in the underwear is dirty. Most children found it no problem to go to toilets somewhere else then at home, but the toilet at school is perceived as unclean. The vast majority of children indicated that fecal incontinence did not result in fewer friends. Bullying by other children was reported by 23% of all children. Children did not miss out on hobbies or social events, but for half of the children their defecation problem did cause problems with these events.

**DISCUSSION**

The present study shows that higher frequency of fecal incontinence is associated with lower HQoL regarding emotional and social functioning in children with constipation. Children reported relatively more emotional concerns about experiencing fecal incontinence than social consequences. Dirty and smelling underwear is distressing to children, as they reported to worry a lot about experiencing fecal incontinence unnoticeably and during school time or about other people smelling them. They are conscious of the fact that their defecation problem causes problems when going on school camp or holidays. This supports previous studies in which parents reported higher rates of internalizing problems such as anxiety and depression symptoms in children with fecal incontinence. In contrast to their worries, half of the children reported hardly to be ashamed of their fecal incontinence. We hypothesize that children have more difficulties with the perception of feelings of shame, while questions about specific worries are more concrete and easier to comprehend.

Although it is generally assumed that fecal incontinence affects social interaction with their peers, most children indicated that they have no problem making friends and not miss out on social events such as hobbies, parties or school camp. On the other hand, 23% of children reported regular bullying by other children because of their defecation problem. This is a higher percentage than reported prevalence rates in Dutch schoolchildren, i.e. 16%, 20% and 12% in children aged 9-11 years, 12-14 years, 15-17 years respectively. In contrast to their worries, half of the children reported hardly to be ashamed of their fecal incontinence. We hypothesize that children have more difficulties with the perception of feelings of shame, while questions about specific worries are more concrete and easier to comprehend.

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The discrepancy between emotional and social concerns raises the question whether children truly experience few social problems. Children’s self-report may be influenced by denial of their defecation problem and the consequences. In our clinic we frequently observe that social consequences are of more concern to the parents than the child. Although we did not measure parents’ perception of HRQoL of their children, previous studies showed that parent’s perceptions of QoL for children with constipation, functional abdominal pain and inflammatory bowel disease were lower than their children’s self-reported scores\textsuperscript{15,24,25}.

The used models for prediction of domain scores by clinical characteristics showed a low goodness of fit, indicating that other factors than fecal incontinence frequency also influenced these scores. Future research should take effects of defensiveness into account, such as denial and social desirability. However, it is known that circumventing these effects of defensiveness has its own difficulties\textsuperscript{26}.

Some limitations of the study need to be addressed. Firstly, we found low reliability of two domains in contrast to sufficient reliabilities described by Voskuil et al\textsuperscript{16}. Higher fecal incontinence frequency in the current study can not explain this dissimilarity, as fecal incontinence was not addressed in these two domains. Furthermore, age, duration of symptoms and male:female ratio were not different between the two cohorts. Lower reliabilities may be explained by the fact that the DDL was developed in a cohort more than four times smaller (n=27) than the current study population.

Low internal consistency is an indicator for random error in clustering the questions within a specific domain. Yet, additional factor analysis did not reveal a better classification of items (analysis not shown). As interpretation of HRQoL domains with low internal consistency is not reliable, we excluded these domains from analysis. Moreover, we even question whether the constipation related domain (3 items) truly measures HRQoL. Content reevaluation showed that this domain addresses presence of certain clinical symptoms, e.g. abdominal pain, but not the child’s subjective perception regarding these symptoms. Regarding domain treatment/intervention, two of the three questions that strongly influenced reliability (analysis not shown), addressed the child’s insight in the importance of certain treatment aspects (i.e. application of rectal enemas and visits to the doctor). Seventy-seven percent of participating children were aged between 8 and 12 years and possibly too young to understand these statements.

The fact that the DDL was not validated for use with only two components is a second limitation of this study. Psychometric analysis (test-retest reliability and convergent validity) for this short version of the DDL needs to be repeated.
Until then no comparison with other studies assessing HRQoL with validated tools is possible. It should further be considered to develop a resembling parent proxy form, so that HRQoL of the child by self-report and parent-report can be compared. Furthermore, it needs to be assessed whether this short DDL is suitable for measuring changes of HRQoL in relation to treatment outcome, as successfully treated children will be free of fecal incontinence. Additional use of a generic QoL questionnaire could be useful for comparison between children with constipation and healthy controls or other patient groups with chronic diseases.

In conclusion, frequent episodes of fecal incontinence are associated with lower HRQoL with regard to emotional and functional functioning in children with constipation. Emotional concerns about fecal incontinence were more predominant than social consequences, but one needs to be alert to bullying by peers. Further adjustment to the DDL with thorough evaluation of its validity is needed, as a disease-specific HRQoL questionnaire is a valuable tool to recognize and address the possible impact of chronic constipation on children.
REFERENCES


25. Loonen HJ, Derkx BH, Koopman HM, Heymans HS. Are parents able to rate the symptoms and quality of life of their offspring with IBD? Inflamm Bowel Dis 2002; 8:270-6.

Chapter 7

Health-related Quality of Life in young adults with continuing symptoms of childhood constipation

Marloes E.J. Bongers
Marc A. Benninga
Heleen Maurice-Stam
Martha Grootenhuis

Submitted
ABSTRACT

Background
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. To date, knowledge on HRQoL in adults with persisting childhood constipation is lacking.

Objectives
To investigate HRQoL in adults with constipation since early childhood, and to gain insight in specific social consequences related to current symptoms in these adult patients.

Methods
One HRQoL questionnaire and one self-developed questionnaire focusing on specific consequences of symptoms of constipation continuing into adulthood were administrated to 182 adults with a history of childhood constipation. Successful clinical outcome was defined as a defecation frequency 3 or more times per week with less than 2 episodes of fecal incontinence per month, irrespectively of laxative use. HRQoL of both adults with unsuccessful and successful clinical outcome were compared to that of 361 peers from the general Dutch population.

Results
Twenty-four percent of the participating adults with a history of childhood constipation had unsuccessful clinical outcome at adult age. These adults reported significantly lower HRQoL compared to the comparison group with respect to scores on Bodily pain (mean±SD 77.4±19.6 versus 85.7±19.5, p=0.01) and General Health (67.6±18.8 versus 74.0±18.1, p=0.04). No difference in HRQoL was found between adults with successful clinical outcome and the comparison group. Adults with unsuccessful clinical outcome reported that current symptoms resulted in difficulties with social contact and intimacy in 20% and 12.5%, respectively. Current therapy in these adults consisted more often of self-administered treatment (e.g. diet modifications) (60.4%) than laxatives (20.9%).

Conclusions
Continuing of childhood constipation into adulthood influences HRQoL negatively. Social consequences as a result of these complaints are reported in 20% of these adults.
BACKGROUND

Functional constipation in children is a common disease with a worldwide prevalence of 8.9% (range 0.7-29.6%) [1]. In about a third of children with constipation symptoms continue into adulthood, despite intensive treatment and follow-up [2,3]. Chronic symptoms of constipation, especially frequent episodes of fecal incontinence, are a source of great distress and concern to the child and their family. Besides physical distress, more behavioral problems are reported in children with constipation and fecal incontinence [4-6]. Furthermore, children with functional constipation and their parents reported impaired quality of life in relation to physical complaints and long duration of symptoms [7,8]. Moreover, parent-reported quality of life in children with constipation was even lower than that reported by their children [7]. Only one small study observed a trend for adults with a history of childhood constipation to report lower levels of general health and social functioning when compared with controls [3].

To date, insufficient knowledge exists on the health-related quality of life (HRQoL) of adult patients experiencing constipation since childhood. Therefore, the aim of this study was to compare current HRQoL in young adults with continuing symptoms of childhood constipation to those free of symptoms of constipation on the one hand and peers from the general Dutch population on the other hand. Secondly, we aimed to gain more insight in the specific consequences of continuing symptoms of constipation and/or fecal incontinence at adult age.

METHODS

Procedure

A cross-sectional study was performed at the Department of Pediatric Gastroenterology and Nutrition of the Emma children's hospital/Academic Medical Centre in Amsterdam. Patients were selected from an existing follow-up cohort of children with functional constipation formed between 1991-1999 [2]. Children were included in this follow-up cohort after participation in one of the research protocols on childhood constipation [9,10]. Diagnosis of functional constipation was based on presence of at least two of the following criteria: 1) defecation frequency less than three per week; 2) two or more episodes of fecal incontinence per week; 3) passage of very large amounts of stool once every 7 – 30 days; 4) a palpable abdominal or rectal mass on physical examination [9]. Patients under 5 years of age and/or patients with laxative treatment...
shorter than 2 months prior to inclusion in one of the research protocols were excluded, as those with organic causes of constipation. After ending the 6-8 weeks treatment protocols, follow-up was conducted at 6 months and annually thereafter during a visit to the outpatient clinic or by phone using a standardized questionnaire.

Between 2004 and 2007, patients aged between 18 and 30 years in this cohort were asked during a standard follow-up to participate in this study. Regardless of participating in this study, follow-up was conducted in all contacted patients. Participating patients received two questionnaires by post. After completion at home, these questionnaires could be returned in a stamped addressed envelope provided. In case of no response, the patient was reminded by phone with a maximum of two follow-up calls. Inclusion criteria for participation in the study were: 1) age 18-30 years before 1 January 2007; 2) the ability to read and understand the Dutch language of the questionnaires. Patients refusing to participate were asked to give their reason for declining study participation by phone. All participants signed an informed consent form. The study protocol was approved by the medical ethical committee of the Academic Medical Centre of Amsterdam.

Measures

Quality of life
HRQoL was assessed with the RAND-36. The RAND-36 is a Dutch version of the MOS-SF-36 Health Survey and almost identical to the Dutch SF-36 [11]. The RAND-36 is composed of 36 items with standardized response choices, clustered into eight multi-item scales; Physical Functioning (PF), Social Functioning (SF), Role limitations due to Physical health problems (RP), Role limitations due to Emotional problems (RE), general Mental Health (MH), Vitality (VT), Bodily Pain (BP) and General Health perception (GH). The questions refer to the previous 4 weeks. All raw scale scores are converted to a 0-100 scale, with higher scores indicating a better HRQoL. Missing data on the RAND-36 were imputed at scale level. If less than half the items of a scale was missing, the scale-score was calculated based on items the respondent had completed.

A normative population for the RAND-36 was formed previously, including a sample of 508 young adults from the general Dutch population [12]. As our study population was younger than this normative population, we selected as comparison group for this study those adults who were between 18 and 27 years of age.
Validity and reliability of the RAND scales are satisfactory [13]. We found Cronbach's alphas in the range 0.76-0.87 in the study population and 0.73-0.90 in the comparison group.

**Specification of consequences in relation to persistence of constipation**

A questionnaire was developed to assess consequences related to continuing of constipation into adulthood. Eight questions were based on clinical experience of two of the authors (MAB: pediatric gastroenterologist specialized in functional defecation disorders and MAG: psychologist specialized in psychosocial consequences of chronic diseases). Four questions focused on current complaints and treatment (Q1: What kind of defecation problems do you have currently?; Q2: If still complaints, do you apply any kind of self-treatment?; Q3: If still complaints, are you using medication at this moment? Q4: If still complaints and no current medical treatment; what are the reasons for no treatment?). In addition, patients with unsuccessful clinical outcome were asked whether these complaints accounted for specific social consequences (Q5: How do you feel about talking to others about your problems of constipation and/or fecal incontinence?; Q6: How do you feel about talking to others about the treatment of your problems of constipation and/or fecal incontinence?; Q7: How often did you experience difficulties in social contact caused by problems of constipation and/or fecal incontinence?; Q7: How often did you experience difficulties in intimate contact caused by problems of constipation and/or fecal incontinence?; Q8: If your defecation problems never caused difficulties with intimacy, what was the reason?).

**Medical data**

The following medical data were obtained from the follow-up database at the Department of Pediatric Gastroenterology & Nutrition: *intake characteristics*: age of onset, age, defecation and fecal incontinence frequency, painful defecation and abdominal pain; *last follow-up characteristics*: duration of follow-up, age, defecation and fecal incontinence frequency, painful defecation, abdominal pain and clinical outcome. Clinical outcome at last follow-up was regarded as successful if in the previous 4 weeks defecation frequency was 3 or more times per week with less than 2 episodes of fecal incontinence per month, irrespectively of laxative use. According to this definition, the total group of adults who experienced constipation as a child was divided into two subgroups, i.e. one subgroup of patients with unsuccessful clinical outcome at adult age versus those with successful clinical outcome at adult age.
Statistical Analysis

Descriptive analysis was performed to assess the characteristics of the sample. To detect *a priori* differences between adults with a history of childhood constipation and the comparison group, demographic characteristics were compared using Student’s t-tests for continuous outcomes and Chi-square or Fisher’s exact-tests for dichotomous outcomes. Furthermore, similar tests were used to assess for difference in intake characteristics during the first visit to the outpatient clinic and characteristics at last follow-up for adults with unsuccessful clinical outcome compared to those with successful clinical outcome. Multivariate (MANOVA) and univariate analyses of variance (ANOVA) were conducted to test group differences on the RAND-36 scales, controlled for age at study and gender. Comparison was made between the total study population and the comparison group, but the comparison group was also compared to adults with unsuccessful clinical outcome, as well as adults with successful clinical outcome. Finally, adults with unsuccessful clinical outcome were compared to those with successful clinical outcome. A significant level of 0.05 was used. Effect sizes (d) were calculated by dividing the difference in mean score between groups concerned by the standard deviation of scores in the group allocated as reference. Effect sizes of 0.2, 0.5 and 0.8 were considered small, moderate and large, respectively [14].

Results on the short questionnaire with regard to specific consequences in adults with unsuccessful clinical outcome are given in a descriptive way.

RESULTS

Patient characteristics

From the existing follow-up cohort of 416 children with constipation, 299 patients reached the age of 18 years before January 2007. Of these adults, 68 patients (22.7%) dropped out from the follow-up cohort before 2004 for several reasons: wrongly included in previous research protocols: n=9, protocol violation: n=2, lost to follow-up: n= 56 and diseased: n=1. No significant differences were found in age at intake, gender, age of onset, intake defecation and fecal incontinence frequency between drop-outs of the follow-up cohort compared to those available for follow up.

For this study, 231 young adults of our follow-up cohort were eligible. A total of 182 questionnaires were returned (response 78.8%). Of the 49 adults with childhood constipation not completing the questionnaires (non-responders), 19 (38.8%) did not have enough time or did not feel like participating in the
Table 1. Demographic characteristics of the study population and the comparison group

<table>
<thead>
<tr>
<th></th>
<th>Study Population (n= 182)</th>
<th>Comparison group (n= 361)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age at study (years)</td>
<td>21.4*</td>
<td>2.3</td>
</tr>
<tr>
<td>Age of onset (years)</td>
<td>3.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Age at intake (years)</td>
<td>9.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Follow-up duration (years)</td>
<td>12.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Gender</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Male</td>
<td>58.2**</td>
<td>106</td>
</tr>
<tr>
<td>Female</td>
<td>41.8</td>
<td>76</td>
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<tr>
<td>Native Country</td>
<td>%</td>
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<tr>
<td>The Netherlands</td>
<td>98.9</td>
<td>180</td>
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<tr>
<td>Other</td>
<td>1.1</td>
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*p= 0.001; **p= 0.02

Table 2. Demographic and medical characteristics of the study population according to clinical outcome at last follow-up

<table>
<thead>
<tr>
<th></th>
<th>Unsuccessful (n= 43)</th>
<th>Successful (n= 139)</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
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<tr>
<td>Intake characteristics</td>
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<td>Age of onset (years)</td>
<td>3.9</td>
<td>3.7</td>
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<tr>
<td>Age at intake (years)</td>
<td>10.0*</td>
<td>2.6</td>
</tr>
<tr>
<td>Defecation/ week</td>
<td>2.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Fecal incontinence/ week</td>
<td>13.3</td>
<td>12.5</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Male</td>
<td>44.2**</td>
<td>19</td>
</tr>
<tr>
<td>Large stools</td>
<td>74.4</td>
<td>32</td>
</tr>
<tr>
<td>Painful defecation</td>
<td>54.8</td>
<td>17</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>61.3</td>
<td>19</td>
</tr>
<tr>
<td>Abdominal scybalus</td>
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<td>10</td>
</tr>
<tr>
<td>Rectal scybalus</td>
<td>34.9</td>
<td>15</td>
</tr>
<tr>
<td>Last follow-up characteristics</td>
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<td></td>
</tr>
<tr>
<td>Age at last follow-up (years)</td>
<td>21.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Follow-up duration (years)</td>
<td>11.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Defecation/ week</td>
<td>2.4****</td>
<td>1.5</td>
</tr>
<tr>
<td>Fecal incontinence/ week</td>
<td>0.5****</td>
<td>1.6</td>
</tr>
<tr>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Painful defecation</td>
<td>46.5****</td>
<td>20</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>62.8******</td>
<td>27</td>
</tr>
</tbody>
</table>

*p= 0.02; **p=0.03; ***p< 0.001; ****p=0.001
study. A total of 30 adults (61.2%) agreed to fill out the questionnaires, but failed to return them. There was a higher percentage of women among the respondents compared to the non-responders (41.8% versus 22.4%, p=0.01). Furthermore, at last follow-up, 23.6% of the responders had unsuccessful clinical outcome versus 10.2% of the non-responders (p=0.04). Age of onset and age at intake, defecation and fecal incontinence frequency at intake were not significantly different between responders and non-responders, as well as follow-up duration and age at last follow-up.

The demographic and medical characteristics of the study population and comparison group are given in tables 1 and 2. The total study population appeared to be different from the comparison group with respect to age at study and gender (table 1). Comparison within the study population showed that adults with unsuccessful clinical outcome were older at intake during the first visit to the outpatient clinic than those with successful clinical outcome (table 2). Furthermore, the percentage of males was significantly lower for adults with unsuccessful clinical outcome compared to those with successful clinical outcome. Clinical symptoms of constipation at last follow-up, i.e. defecation and fecal incontinence frequency, and accompanying symptoms such as painful defecation and abdominal pain, differed significantly between adults with unsuccessful clinical outcome compared to those with successful clinical outcome (table 2). Defecation frequency less than twice per week was present in 88% of adults with unsuccessful clinical outcome, while fecal incontinence once per two week or more often occurred in 21%.

Quality of life (RAND-36)

The multivariate analysis of variance (MANOVA) for the RAND scales as a function of group, gender and age showed a main effect on gender (females scored lower than males), but not on group and age at study, for comparison between the total study population and the comparison group (F(8,522) = 4.1, p<0.001). A similar gender effect was also found for comparison between the successful clinical group and comparison group (F(8,479) = 3.0, p=0.003), as well as for the adults with unsuccessful clinical outcome compared to those with successful clinical outcome (F(8,166) = 4.1, p<0.001).

Multivariate main effects on group (F(8,388) = 2.8, p=0.005), gender (F(8,388) = 2.5, p=0.01) and age at study ((F(8,388) = 2.0, p=0.04) were found for comparison between adults with unsuccessful clinical outcome and the comparison group (table 3). Adults with unsuccessful clinical outcome showed worse HRQoL than the comparison group with respect to Bodily pain (F(1,395)
HRQoL in young adults with childhood constipation

Table 3. Mean scores, SD’s and differences between adults with unsuccessful clinical outcome and the comparison group on the eight scales of the RAND-36

<table>
<thead>
<tr>
<th>Scale</th>
<th>Unsuccessful males (n=19)</th>
<th>Unsuccessful females (n=24)</th>
<th>Unsuccessful total (n=43)</th>
<th>Comparison group males (n=169)</th>
<th>Comparison group females (n=187)</th>
<th>Comparison group total (n=356)</th>
<th>Effect size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF</td>
<td>98.2</td>
<td>86.7</td>
<td>91.7</td>
<td>94.0</td>
<td>92.2</td>
<td>93.1</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>4.2</td>
<td>16.8</td>
<td>14.0</td>
<td>13.6</td>
<td>14.7</td>
<td>14.0</td>
<td></td>
</tr>
<tr>
<td>SF</td>
<td>88.8</td>
<td>81.3</td>
<td>84.6</td>
<td>88.7</td>
<td>84.0</td>
<td>86.5</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>21.2</td>
<td>24.5</td>
<td>23.1</td>
<td>18.2</td>
<td>20.5</td>
<td>19.3</td>
<td></td>
</tr>
<tr>
<td>RP</td>
<td>97.4</td>
<td>88.5</td>
<td>92.4</td>
<td>90.7</td>
<td>82.5</td>
<td>86.8</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>7.9</td>
<td>22.1</td>
<td>17.7</td>
<td>21.6</td>
<td>31.7</td>
<td>27.0</td>
<td></td>
</tr>
<tr>
<td>RE</td>
<td>89.5</td>
<td>90.3</td>
<td>89.9</td>
<td>88.2</td>
<td>82.6</td>
<td>85.5</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>27.3</td>
<td>25.0</td>
<td>25.8</td>
<td>28.9</td>
<td>32.8</td>
<td>30.8</td>
<td></td>
</tr>
<tr>
<td>MH</td>
<td>78.7</td>
<td>72.5</td>
<td>75.3</td>
<td>76.8</td>
<td>73.0</td>
<td>75.1</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>16.7</td>
<td>15.1</td>
<td>15.9</td>
<td>15.6</td>
<td>16.5</td>
<td>15.9</td>
<td></td>
</tr>
<tr>
<td>VT</td>
<td>68.5</td>
<td>60.4</td>
<td>64.0</td>
<td>66.9</td>
<td>61.7</td>
<td>64.5</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>18.3</td>
<td>16.6</td>
<td>17.7</td>
<td>16.6</td>
<td>18.3</td>
<td>17.4</td>
<td></td>
</tr>
<tr>
<td>BP</td>
<td>87.9</td>
<td>69.1</td>
<td>77.4*</td>
<td>89.0</td>
<td>82.9</td>
<td>85.7</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>15.0</td>
<td>19.0</td>
<td>19.6</td>
<td>16.1</td>
<td>21.6</td>
<td>19.5</td>
<td></td>
</tr>
<tr>
<td>GH</td>
<td>74.7</td>
<td>61.9</td>
<td>67.6**</td>
<td>75.0</td>
<td>72.9</td>
<td>74.0</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>17.6</td>
<td>18.1</td>
<td>18.8</td>
<td>17.0</td>
<td>18.9</td>
<td>18.1</td>
<td></td>
</tr>
</tbody>
</table>

1 Multivariate effects were found on group (p=0.005), gender (p=0.01) and age at study (p=0.04). *p=0.01 and **p=0.04: difference between adults with unsuccessful clinical outcome and the comparison group (based on univariate F-tests according to MANOVA by group, gender, age). PF: physical functioning; SF: social functioning; RP: role limitations due to physical problems; RE: role limitations due to emotional problems; MH: mental health; VT: vitality; BP: bodily pain; GH: general health perceptions.

= 6.4, p=0.01) and General health perception (F(1,395) = 4.5, p=0.04). Effect sizes for these significant differences were 0.43 and 0.35, respectively.

Specific consequences in adults with unsuccessful clinical outcome

In the 43 adults with continuing of childhood constipation at adult age, self-reported complaints were constipation in 76.7% and fecal incontinence with or without low defecation frequency in 14% (table 4). Four adults regarded themselves as free of symptoms, despite the fact that two of them had a low
Table 4. Self-reported frequencies of specific consequences in adults with unsuccessful clinical outcome

<table>
<thead>
<tr>
<th>Consequence</th>
<th>Unsuccessful (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
</tr>
<tr>
<td>1) Type of symptoms still present</td>
<td></td>
</tr>
<tr>
<td>constipation</td>
<td>76.7</td>
</tr>
<tr>
<td>fecal incontinence</td>
<td>7.0</td>
</tr>
<tr>
<td>both</td>
<td>7.0</td>
</tr>
<tr>
<td>none</td>
<td>9.3</td>
</tr>
<tr>
<td>2) Self treatment for symptoms</td>
<td></td>
</tr>
<tr>
<td>diet</td>
<td>48.8</td>
</tr>
<tr>
<td>toilet training</td>
<td>11.6</td>
</tr>
<tr>
<td>none</td>
<td>39.5</td>
</tr>
<tr>
<td>3) Treatment with laxatives for symptoms</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>20.9</td>
</tr>
<tr>
<td>no</td>
<td>79.1</td>
</tr>
<tr>
<td>4) Reason no medical treatment for symptoms</td>
<td></td>
</tr>
<tr>
<td>do not feel like it</td>
<td>9.1</td>
</tr>
<tr>
<td>do not know who or where to go to</td>
<td>15.2</td>
</tr>
<tr>
<td>not necessary</td>
<td>66.7</td>
</tr>
<tr>
<td>other reasons</td>
<td>9.1</td>
</tr>
<tr>
<td>5) Feelings regarding talking to others about symptoms</td>
<td></td>
</tr>
<tr>
<td>(very) difficult</td>
<td>10.0</td>
</tr>
<tr>
<td>somewhat difficult</td>
<td>15.0</td>
</tr>
<tr>
<td>not at all difficult</td>
<td>35.0</td>
</tr>
<tr>
<td>do not talk about it</td>
<td>40.0</td>
</tr>
<tr>
<td>6) Feelings regarding talking to others about treatment</td>
<td></td>
</tr>
<tr>
<td>(very) difficult</td>
<td>7.5</td>
</tr>
<tr>
<td>somewhat difficult</td>
<td>7.5</td>
</tr>
<tr>
<td>not at all difficult</td>
<td>25.0</td>
</tr>
<tr>
<td>do not talk about it</td>
<td>60.0</td>
</tr>
<tr>
<td>6) Frequency of difficulties with social contact, related to symptoms</td>
<td></td>
</tr>
<tr>
<td>(very) often</td>
<td>15.0</td>
</tr>
<tr>
<td>Sometimes</td>
<td>5.0</td>
</tr>
<tr>
<td>never</td>
<td>80.0</td>
</tr>
<tr>
<td>7) Frequency of difficulties with intimacy, related to symptoms</td>
<td></td>
</tr>
<tr>
<td>(very) often</td>
<td>2.5</td>
</tr>
<tr>
<td>sometimes</td>
<td>10.0</td>
</tr>
<tr>
<td>never</td>
<td>87.5</td>
</tr>
<tr>
<td>8) Reason symptoms never a problem with intimacy</td>
<td></td>
</tr>
<tr>
<td>partners understand symptoms</td>
<td>47.1</td>
</tr>
<tr>
<td>hiding my symptoms</td>
<td>11.8</td>
</tr>
<tr>
<td>no fecal incontinence; thus no influence of symptoms on intimacy</td>
<td></td>
</tr>
<tr>
<td>never been intimate with someone</td>
<td>14.7</td>
</tr>
</tbody>
</table>
defecation frequency (2 times per week) and the other two still experienced fecal incontinence with a frequency of two times per week and once per 2 weeks, respectively. The percentage of adults that administered self treatment, i.e. dietary measurements or toilet training, was high compared to the percentage using laxatives (60.6% versus 20.9%). Medical treatment was regarded as not necessary by 66.7% of the adults with unsuccessful clinical outcome. Twenty-five percent of adults found it difficult to talk about the persisting symptoms with others and 15% experiencing difficulties when talking about treatment of these symptoms. Problems with social contacts caused by constipation and/or fecal incontinence were reported by 20% of these adults and 12.5% indicating to have had negative experiences in relation to intimacy.

DISCUSSION

This study assessed Health-related Quality of Life in a cohort of adults with a history of functional childhood constipation. Symptoms continued into adulthood in 24% of children with constipation. Unsuccessful clinical outcome at adult age was associated with lower HRQoL with regard to general health and bodily pain compared to healthy controls. Furthermore, unsuccessful clinical outcome resulted in social consequences in one-fifth of adults with persistence of symptoms. Adults still experiencing symptoms of constipation and/or fecal incontinence applied more often self-administered treatments than laxatives. Our data confirms previous findings in smaller cohort studies that childhood constipation continues into adulthood in approximately a quarter of patients [2,3]. Even after all these years, 88% of adults with unsuccessful clinical outcome experienced a low defecation frequency and fecal incontinence was still present in 21%. In addition, accompanying symptoms of constipation such as painful defecation and abdominal pain were approximately twice as common in adults with unsuccessful clinical outcome as in those free of constipation. Remarkably, only one out of five adults with unsuccessful clinical outcome still used laxatives and 66% found medical treatment no longer necessary. Different reasons may explain these results. On the one hand, these adults with a history of constipation going back to childhood may have adapted to the condition. Self-report of these adults indeed indicated that the vast majority experienced no social consequences. This is further underlined by the fact that we found no impairment of QoL on social, emotional or mental health scales in adults with persisting gastrointestinal symptoms, in contrast to several studies in patients with onset of functional gastrointestinal diseases at adult age [15-18]. However, comparison with some adult studies should be considered with
caution since age and sex distributions were different to our study population [17,18]. Furthermore, we suggest that in most adults, in contrast to childhood, fecal incontinence was no longer a predominant symptom and this may have limited impact on social and emotional functioning. On the other hand, adults with persisting constipation and/or fecal incontinence may avoid medical treatment out of shame or denial because these symptoms are still present at adult age. After years of unsuccessful treatment, disappointment in medical care may have been another reason for these adults to avoid medical care. Furthermore, the fact that 15% of adults did not know to who or where to go to for treatment leaves room open for improvement of transition to adult care.

Adults with unsuccessful clinical outcome had poorer HRQoL, especially in general health perception and bodily pain, compared to peers. A lower score for general health perception indicates that patients were more concerned about their health than were adults in the norm population. To date, only one study has reported on HRQoL in adults with a history of childhood constipation and found a trend of lower levels of general health and social functioning in these adults compared to controls [3]. However, comparison with our findings is hampered, as Khan et al. used a small sample of 20 adults without making a distinction between adults still constipated and those free of complaints [3]. Yet, lower general health is also reported in several studies in adults with functional constipation, as well as adults with (constipation predominant) IBS [19-22].

Worse score on bodily pain in these adults with persisting symptoms of childhood constipation may be explained by the high frequency of pain complaints, i.e. painful defecation and abdominal pain. This finding seems in line with previous studies reporting impaired QoL in children with functional constipation and those with functional abdominal pain [7,23]. In children with chronic gastrointestinal disorders, low self-reported physical scores, containing questions regarding “ache or hurt”, may be a reflection of years of painful defecation and abdominal pain. Similarly, studies in adults with functional constipation or IBS found that painful defecation and abdominal pain were strongly associated with impaired QoL [16,19,21,24].

QoL has been evaluated in other patient groups reporting defecation problems starting in early childhood and continuing into adulthood, i.e. Hirschsprung’s disease and anorectal malformations [25]. Both of these patient groups, showed lower physical health, which was not found in our study population. In line with our findings, patients with anorectal malformations reported impaired QoL with respect to general health and pain level [25]. Remarkably, not disease-specific factors like constipation and fecal incontinence, but factors as self-esteem and social support were main mediating factors affecting generic QoL [25]. Yet, it
is questionable whether you can compare HRQoL outcome of patients with congenital diseases to those with a functional gastrointestinal disorder. No overall significant difference in HRQoL scores was found between successfully and unsuccessfully treated adults. However, in contrast to adults with persisting symptoms, scores on bodily pain and general health perception for successful clinically treated adults were comparable to healthy controls (Bodily pain: 86.8 versus 85.7; General health: 72.8 versus 73.9, respectively). This finding seems to support that impaired HRQoL found in adults with unsuccessful clinical outcome is related to the persistence of symptoms. Some limitations of the study need to be considered. Our findings could be biased due to lost to follow-up in our cohort, as we do not know whether these drop-outs were more or less likely to have achieved successful clinical outcome. Achievement of success at a young age may have been a reason for patients to refuse further participation in our long-term follow-up study. On the other hand, unsuccessfully treated patients may have declined further participation out of disappointment with medical treatment. Furthermore, our findings are possible biased by the fact that the percentage of adults with unsuccessful clinical outcome was higher among responders than among non-responders. However, this bias is most likely limited as overall response rate of the study was high and the responders group still consisted of three times more successfully treated adults than those with persisting symptoms. Finally, no correction for other factors potentially influencing HRQoL was made. It has been suggested that psychosocial factors such as anxiety/depression, self-esteem and social support could well affect patient-perceived health status [25-27]. Further analysis of patients’ psychosocial functioning, whether or not related to constipation, in our study population may give more insight in interaction between these aspects of health.

CONCLUSIONS

Functional constipation in children is not always a benign condition with favorable outcome, as symptoms persist into young adulthood in approximately a quarter of these children. Persistence of childhood constipation into adulthood is associated with impaired HRQoL at adult age. Symptoms may even affect social contacts in a fifth of adults with unsuccessful clinical outcome. Further quantification of this burden is needed to determine the best course for prevention and treatment strategies.
Acknowledgements
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REFERENCES


Chapter 8

Course of life in young adults with a history of childhood constipation

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Marc A. Benninga
Heleen Maurice-Stam
Martha Grootenhuis

Submitted
ABSTRACT

Background & Aims
In a substantial subgroup of children, functional constipation is a chronic disorder which may influence children’s psychosocial development. This study aimed to evaluate autonomy, psycho-sexual and social development and socio-demographic outcomes in young adults with a history of childhood constipation with or without fecal incontinence.

Methods
At a Dutch tertiary centre, a cross-sectional study was performed in a long-term follow-up cohort of children with functional constipation. A total of 181 patients from this cohort, aged between 18 and 30 years, and 361 young adults from the general Dutch population filled out the Course of Life questionnaire.

Results
Compared to controls, course of life was delayed in adults with a history of childhood constipation. They achieved fewer milestones with respect to autonomy and social development. Delayed course of life was especially found in a subgroup of these adults who experienced fecal incontinence up to a maximum of 18 years, but not in adults who never experienced fecal incontinence or not after the age of 12. Educational level was lower among adults with a history of childhood constipation than among controls, and unemployment rate was higher.

Conclusions
Autonomy and social development of young adults grown up with functional constipation was delayed, especially in those with long duration of constipation-associated fecal incontinence up to adolescent age. Clinicians should encourage parents in stimulating their child in these areas. The impact of lower socioeconomic status in adults with a history of childhood constipation on course of life needs to be further evaluated.
INTRODUCTION

Functional constipation in children is a common disease with a worldwide prevalence of 8.9% (range 0.7-29.6%)\(^1\). Main symptoms in children with constipation are a low defecation frequency, hard stools, painful defecation and frequent episodes of fecal incontinence. Other frequently accompanying symptoms of childhood constipation are abdominal pain, poor appetite and urinary incontinence\(^2,\,3\). The underlying pathophysiology is still not fully understood. Treatment of childhood constipation is therefore mainly symptomatic consisting of education, behavioral advices such as toilettraining and laxatives\(^4,\,5\). Despite intensive treatment and follow-up, 25-30% of children with constipation experience persistence of symptoms into adulthood\(^6,\,7\).

Growing up with a chronic disease or with chronic constipation may influence the child’s psychosocial development, such contacts and interaction with peers or becoming independent. Fulfillment of age-specific developmental tasks and achievement of developmental milestones during childhood and adolescence, referred to as ‘course of life’, are of great importance to the adjustment to later adult life\(^8,\,9\). A hampered course of life was found in young adults with chronic diseases during childhood, like cancer, end stage renal disease, and organic causes of chronic constipation and fecal incontinence (i.e Hirschsprung’s disease and anorectal malformations)\(^10\). In those adults growing up with Hirschsprung’s disease or anorectal malformations, psychosexual development was found to be impaired, while patients who grew up with anorectal malformations also reported less favorable social development and less achievement of autonomy milestones.

To date, no knowledge exists on the achievement of developmental milestones of young adults grown up with functional constipation. Suffering from constipation and fecal incontinence may lead to decreased participation in both school-based and after school activities, e.g. participating in (school) sports, playing with friends. Distress of experiencing fecal incontinence during adolescence may negatively affect peer interaction and sexual development. Long-term symptoms and treatment of children with constipation can increase parental concerns and involvement, possible limiting the child’s acquisition of independence. Therefore, the aim of this study was to compare the autonomy, psycho-sexual and social development and socio-demographic outcomes in young adults with childhood constipation to a reference group of young adults from the Dutch population. Furthermore, the relationship between these developmental outcomes on the one hand and experiencing fecal incontinence during specific age periods (childhood and/or adolescence) on the other hand was evaluated.
METHODS

Procedure
A cross-sectional study was performed at the Department of Pediatric Gastroenterology and Nutrition of the Emma Children’s Hospital/Academic Medical Centre in Amsterdam. Patients were selected from an existing follow-up cohort of children with functional constipation formed between 1991-1999. Children were included in this follow-up cohort after participation in one of the research protocols on childhood constipation. Diagnosis of functional constipation was based on presence of at least two of the following criteria: 1) defecation frequency less than three per week; 2) two or more episodes of fecal incontinence per week; 3) passage of very large amounts of stool once every 7 – 30 days; 4) a palpable abdominal or rectal mass on physical examination. Patients under 5 years of age and/or patients with laxative treatment shorter than 2 months prior to inclusion in one of the research protocols were excluded, as those with organic causes of constipation. After ending the 6-8 weeks treatment protocols, follow-up was conducted 6 months and annually thereafter during a visit to the outpatient clinic or by phone using a standardized questionnaire.

Between 2004 and 2007, patients aged between 18 and 30 years in this cohort were asked during standard follow-up to participate in this study by filling out the Course of Life questionnaire. After completion at home, the questionnaire could be returned in a stamped addressed envelope provided. In case of no response, the patient was reminded by phone with a maximum of two follow-up calls. Inclusion criteria for participation in the study were: 1) age 18-30 years before 1 January 2007; 2) the ability to read and understand the Dutch language of the questionnaire. Patients who did not want to participate were asked to give their reason for declining study participation by phone. All patients declining to fill in the Course of Life questionnaire did however answer questions regarding their defecation pattern. Therefore medical follow-up was conducted in all contacted patients. All participants signed an informed consent form. The study protocol was approved by the medical ethical committee of the Academic Medical Centre of Amsterdam.

Measures
Course of life
The Course of life questionnaire, a Dutch questionnaire developed by the Psychosocial department of the Emma children’s hospital/Academic Medical Centre, was used to retrospectively assess achievement of developmental
milestones in children. This instrument was developed to assess the course of life of young adults, aged between 18 and 30 years, who grew up with a chronic or life-threatening disease, in comparison with the course of life of peers without a history of disease. Most questions retrospectively ask whether the respondent has achieved factual developmental milestones (yes, no), or at which age (category) the respondent achieved the milestones. Questions do not go further back in time than primary school. Answers are dichotomized, where necessary, before being added to the scale-score. For this study, three scales of the Course of life questionnaire were used: (1) development of autonomy (6 items about autonomy at home and outside home; (2) psycho-sexual development (4 items about love and sexual relations); (3) social development (12 items about social contacts with peers, at school and in leisure time). A higher score on the scales indicates the accomplishment of more developmental milestones and therefore a more favorable course of life. Apart from these scales, the questionnaire measures social-demographic outcomes in young adulthood, such as living situation, education, and employment.

A normative population for the Course of life questionnaire was formed previously, including a sample of 508 young adults from the general Dutch population. As our study population was younger than this normative population, we selected adults in the comparable age range. Thus we included only those adults who were between 18 and 27 years of age as reference group for this study (n=361).

Validity, test-retest reliability and internal consistency of the Course of life scales are good, except for moderate internal consistency of the autonomy scale. Items in this scale concern diverging aspects of autonomy. The Cronbach’s alphas in the population under study were low to good: (1) development of autonomy: study population 0.39, reference 0.50; (2) psycho-sexual development: study population 0.77, reference 0.70; (3) social development: study population 0.78, reference 0.71. The use of scales with low to moderate internal consistency is acceptable for group comparisons because internal consistency is an indication of random error and has nothing to do with systematic error (bias).

Medical data

The following medical data were obtained from the follow-up database at the Department of Pediatric Gastroenterology & Nutrition: intake characteristics: age of onset, age, defecation frequency, fecal incontinence frequency, passage of large stools, presence of abdominal and/or rectal mass, duration of symptoms before intake; follow-up characteristics: duration of follow-up, age at last follow-up, presence of fecal incontinence at each follow-up moment.
Patients were categorized in subgroups based on the age at which they experienced fecal incontinence during childhood: 1) < age 6 years or never; 2) up to a maximum of 12 years; 3) up to a maximum of 18 years.

Statistical Analysis
Descriptive analysis was performed to assess the characteristics of the sample. To detect a priori differences between adults with childhood constipation and the reference group, demographic characteristics were compared using Student’s t-test and Chi-square-test.
Univariate analyses of variance (ANOVA) were conducted to test group differences on the three Course of life scales, controlled for age at study and gender. Effect sizes (d) on the course of life scales were calculated by dividing the differences in mean score between adults with childhood constipation (total study population and subgroups categorized by age of experiencing fecal incontinence) and reference group by the standard deviation of the scores in the reference group. Effect sizes of 0.2, 0.5 and 0.8 were considered small, moderate and large, respectively.

In order to gain detailed insight into the course of life of the participants, logistic regression with correction for age at study and gender was conducted to determine the main effect of group (total study population versus the reference group) on items of the scales on which significant differences between groups were found. In addition, logistic regression was conducted to determine differences between groups (total study population versus the reference group) in living situation, marital status, educational level (dichotomized: low versus middle/high) and occupational status, taking gender and age at study into account. Item frequencies and percentages are reported in a descriptive way.

Due to the explorative nature of this study, priority was given to find phenomena that exist (avoiding type II errors) rather than correcting for multiple testing (avoiding type I errors). Therefore, a significant level of 0.05 was used for all analyses.

RESULTS
Population
From the existing follow-up cohort of 416 children with constipation, 299 patients reached the age of 18 years before January 2007. Of these adults, 68 patients (22.7%) dropped out from the follow-up cohort before 2004 for several reasons.
reasons: wrongly included in previous research protocols: n=9, protocol violation: n=2, lost to follow-up: n=56 and diseased: n=1. No significant differences were found in gender, age of onset, age, defecation and fecal incontinence frequency at first visit to the outpatient clinic between drop-outs of the follow-up cohort compared to those available for follow up.

For this study, 231 young adults of the follow-up cohort were eligible. A total of 181 patients (58.0% males, mean (±SD) duration of follow-up 12.2 (±1.8) years) returned the questionnaire (response 78.3%). Clinical characteristics at first visit to the outpatient clinic of these young adults are shown in table 1. During childhood, fecal incontinence was never experienced or no longer present from the age of 6 years in 12% of patients, while 41% of patients

| Table 1. Demographic and clinical characteristics of the study population and reference |
|---------------------------------------------------------------|-----------------|-----------------|-----------------|
| Demographic characteristics                                  | Study Population | Reference       |
|                                                              | Mean (SD)       | Range           | Mean (SD)       | Range           |
| Age at study (years)*                                        | 21.4 (2.3)      | 17.7-27.8       | 22.2 (2.5)      | 18.0-27.0       |
| % N                                                           | % N             |                 | % N             |                 |
| Gender**                                                      |                 |                 |                 |
| Male                                                         | 58.0 (105)      | 47.1 (170)      |
| Female                                                       | 42.0 (76)       | 52.9 (191)      |
| Native Country                                               |                 |                 |                 |
| The Netherlands                                             | 98.9 (179)      | 97.2 (351)      |
| Other                                                        | 1.1 (2)         | 2.8 (10)        |
| Educational level parents**                                  |                 |                 |                 |
| Low                                                          | 35.8 (59)       | 36.8 (125)      |
| Middle                                                       | 38.8 (64)       | 27.4 (93)       |
| High                                                         | 25.5 (42)       | 35.9 (122)      |
| Clinical characteristics at first visit to clinic            |                 |                 |                 |
| Age (years)                                                  | 9.2 (2.4)       | 5.1-17.1        |
| Age at onset of constipation (years)                         | 3.3 (2.8)       | 0.0-12.0        |
| Duration of symptoms before intake (years)                   | 5.9 (3.1)       | 0.3-16.1        |
| Defecation frequency / week                                  | 2.9 (3.2)       | 0.0-16.0        |
| Fecal incontinence frequency / week                          | 13.1 (11.2)     | 0.0-56.0        |
| % N                                                          |                 |                 |                 |
| Passage of large stools                                      | 64.6 (117)      |
| Abdominal scybalus                                           | 21.5 (39)       |
| Rectal scybalus                                              | 28.7 (52)       |
| Age of experiencing fecal incontinence#                     | % N             |                 |
| < age 6 years or never                                       | 11.6 (21)       |
| up to a maximum of 12 years                                  | 40.9 (74)       |
| up to a maximum of 18 years                                  | 47.5 (86)       |

*p = 0.001, Student’s T-test; **p = 0.02, Chi-square test. # during childhood
experienced fecal incontinence up to a maximum age of 12 compared to 48% with fecal incontinence up to a maximum age of 18 (table 1). Of the 50 adults with childhood constipation who did not complete the questionnaires (non-responders), 19 (38.0%) did not have enough time or did not feel like participating in the study and 31 (62.0%) agreed to fill out the questionnaires, but failed to return them. There was a higher percentage of women among the respondents compared to the non-responders (42.0% versus 22.0%, p=0.01). Age of onset and age, defecation and fecal incontinence frequency at first visit to the outpatient clinic were not significantly different between responders and non-responders, as well as follow-up duration and age at last follow-up (data not shown).

The reference group appeared to be different from the study population with respect to age, gender and educational level of their parents (table 1).

Course of life scales: autonomy, psycho-sexual and social development

**Total study population versus the reference group**

Adults grown up with childhood constipation had significantly lower scale scores on autonomy development (F(1,529)=9.9, p=0.002) and social development (F(1,489)=5.5, p=0.02), than the reference group (table 2). The

| Table 2. Mean scores, SD’s and differences between study population (total and subgroups) and reference on three scales of the Course of life questionnaire |
|-------------------------------------------------|------------------|-----------------|------------------|-----------------|-----------------|
| Study Population Age experiencing fecal incontinence | Reference Mean | SD | Effect size (d)1 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| <6 y or Never   | ≤ 12 y          | ≤ 18 y          | Total           | Total           | Total           |
| Autonomy        |                  |                  |                 |                 |                 |
| development     |                  |                  |                 |                 |                 |
| n= 21           | n= 69           | n= 85           | n= 175          | n= 358          |
| Mean            | 9.10            | 8.93            | 8.71**          | 8.84**          | 9.33            | 0.33            |
| SD              | 1.51            | 1.51            | 1.26            | 1.39            | 1.50            |
| Psycho-sexual   |                  |                  |                 |                 |                 |
| development     |                  |                  |                 |                 |                 |
| n= 21           | n= 70           | n= 85           | n= 176          | n= 353          |
| Mean            | 7.38            | 7.19            | 7.18            | 7.20            | 7.17            | 0.03            |
| SD              | 1.02            | 1.22            | 1.26            | 1.21            | 1.12            |
| Social          |                  |                  |                 |                 |                 |
| development     |                  |                  |                 |                 |                 |
| n= 20           | n= 63           | n= 76           | n= 159          | n= 334          |
| Mean            | 21.65           | 20.62           | 20.37*          | 20.63*          | 21.13           | 0.21            |
| SD              | 1.73            | 2.73            | 3.01            | 2.78            | 2.40            |

*p<0.05; **p<0.01; univariate ANOVA’s of Course of life scales by group, gender and age at study. 1 Effect sizes for comparison between total study population and reference.
differences between adults with a history of childhood constipation and the reference group were small: effect sizes (d) of 0.33 and 0.21 respectively. In addition, a main effect of age at study was found on social development (F(1,489)=4.1, p=0.04). Older participants (both in the study population and the reference group) had reached more social developmental milestones. No differences were found for psycho-sexual development.

Subgroups of study population versus the reference group
Significantly lower scores, with small effect sizes, on autonomy (F(1,439)=10.7, df=1, p=0.001, d= 0.42) and social development (F(1,406)=6.1, df=1, p=0.01, d= 0.32) were found among adults who experienced fecal incontinence up to a maximum of 18 years of age than among the reference group (table 2). Adults with no history of fecal incontinence or those who experienced fecal incontinence up to a maximum age of 12 years showed no difference in developmental achievements compared to the reference group.

Course of life on item level
Table 3 shows the individual milestones frequencies of the Course of life scales autonomy and social development for both the total study population and their healthy peers. With respect to autonomy development, a significant predictive effect of group was found on two items. A lower percentage of the study population than the reference group had a regular task in their family during secondary school (odds ratio=0.66, 95%CI (0.46-0.96), p=0.03). In addition, gender was a significant predictor of this item, with males reporting a regular task in their family during secondary school less often than females (odds ratio=0.64, 95%CI (0.45-0.91), p=0.01). The study population reported that they went less often on holiday without adults before the age of 17 years than the reference group (odds ratio=0.68, 95%CI (0.47-0.98, p=0.04). A younger age at intake was also predictive for a lower percentage of going on holiday without adults (odds ratio= 0.93, 95%CI (0.87-0.99), p=0.04).

On three out of the 12 items of social development, group was a significant predictive factor for the difference between the study population and the reference group During primary school, a lower percentage of the study population spent their playing time with friends compared to the reference group (odds ratio=0.38, 95%CI (0.23-0.63), p<0.001). Furthermore, a lower percentage of the study population than the reference group had been a member of a sports club for at least a year during secondary school (odds ratio=0.44, 95%CI (0.30-0.66), p<0.001). Being member of a sports club for at least a year was also lower in the study population for the period after
<table>
<thead>
<tr>
<th></th>
<th>Study population</th>
<th>Reference</th>
</tr>
</thead>
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<tr>
<td></td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>a) Autonomy development</td>
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<tr>
<td>Regular task in your family, primary school</td>
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<tr>
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<td>38.5</td>
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<td>72.2</td>
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<td>49.7*</td>
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<td>For the first time being on holiday without adults</td>
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<td>85</td>
</tr>
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<td>b) Social development</td>
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<td>At least one year of membership in a sports club, primary school</td>
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</tr>
<tr>
<td>yes</td>
<td>81.8</td>
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</tr>
<tr>
<td>no</td>
<td>18.2</td>
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</tr>
<tr>
<td>Number of friends in first-third grade, primary school</td>
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<tr>
<td>less than 4</td>
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<td>4 or more</td>
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<tr>
<td>Number of friends in fourth-sixth grade, primary school</td>
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<td>less than 4</td>
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<tr>
<td>4 or more</td>
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<td>Best friend, primary school</td>
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<tr>
<td>yes</td>
<td>71.8</td>
<td>130</td>
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<tr>
<td>no</td>
<td>28.2</td>
<td>51</td>
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<td>Most of the time playing with ..., primary school friends</td>
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<tr>
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<td>79.2**</td>
<td>141</td>
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<tr>
<td>no</td>
<td>20.8</td>
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<td>At least one year of membership in a sports club, secondary school</td>
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</tr>
<tr>
<td>yes</td>
<td>59.8**</td>
<td>107</td>
</tr>
<tr>
<td>no</td>
<td>40.2</td>
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<td>Number of friends, secondary school</td>
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<td>4 or more</td>
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<td>Best friend, secondary school</td>
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<td>Going out to a bar or disco, secondary school</td>
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<td>sometimes / often</td>
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<td>144</td>
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<tr>
<td>never</td>
<td>20.4</td>
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<td>At least one year of membership in a sports club, after secondary school</td>
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<td></td>
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<tr>
<td>yes</td>
<td>32.2**</td>
<td>56</td>
</tr>
<tr>
<td>no</td>
<td>67.8</td>
<td>118</td>
</tr>
</tbody>
</table>

*p<0.05; **p<0.001: Significance for group according to logistic regression corrected for age at study and gender.

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secondary school (odds ratio=0.48, 95%CI (0.33-0.71) p<0.001). Besides this predictive effect of group, gender was another significant predictor of this item, with males being more often member of a sport club after secondary school than females (odds ratio=1.53, 95%CI (1.07-2.18), p<0.02).

**Socio-demographic outcomes**

Socio-demographic outcomes of the total study population and the reference group are depicted in table 4. Still living with their parents was significantly associated with age at study and gender (odds ratio=0.74, 95%CI (0.29-0.63) and odds ratio=1.6, 95%CI (1.4-1.7) respectively; p<0.001), but not with group. For both young adults in the study population as those in the reference group, it was found that younger participants and males more frequently still lived at home with their parents. Similarly, the percentage of adults being single was predicted by age at study (odds ratio=1.56, 95%CI (1.40-1.73), p<0.001) and gender (odds ratio=0.46, 95%CI (0.29-0.74), p=0.002), showing that the percentage of singles was for higher younger participants and males. No association with group was found. The highest completed level of education was lower for the study population than the reference group (low educational level: 51.2% versus 29.2), with group being a significant predictor

<table>
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<th>Table 4. Percentage and differences between study population and reference group in socio-demographic outcomes</th>
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<td>Study population</td>
</tr>
<tr>
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<tr>
<td><strong>Living with their parents</strong></td>
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<tr>
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</tr>
<tr>
<td><strong>Marital status</strong></td>
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<td>Single</td>
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<tr>
<td><strong>Educational level</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>low</td>
</tr>
<tr>
<td>middle</td>
</tr>
<tr>
<td>high</td>
</tr>
<tr>
<td><strong>Employment status</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
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<td>employed</td>
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<tr>
<td>not employed</td>
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</table>

<sup>**p<0.001; Significance for group according to logistic regression corrected for age at study and gender. 1 Highest level completed: Low: primary education, technical and vocational education, lower and middle general secondary education Middle: Middle vocational education, higher general secondary education, pre-university education High: Higher vocational education, University 2 Students excluded**</sup>
DISCUSSION

To our knowledge, this is the first study addressing the achievement of developmental milestones and the current socio-demographic outcome in a cohort of young adults grown up with functional childhood constipation. These adults reported a delayed course of life compared to that of the reference group, as they achieved fewer milestones on autonomy and social development than their peers. Furthermore, a delayed course of life was especially found in the subgroup of adults with fecal incontinence up to a maximum of 18 years of age, but not in adults who never experienced fecal incontinence or those without fecal incontinence after the age of 12. With regards to socio-demographic outcomes, our study population, showed lower educational level than the reference group, while unemployment rate was higher.

In line with our hypothesis a delayed course of life was found in adults who experienced constipation during childhood, especially during adolescence. A less favorable course on autonomy and social development could have great implications. It is well-known that achievement of developmental milestones in youth is of importance in the adjustment to adult life. In our study, children and adolescents grown up with constipation reported less playing with friends during primary school and less participation in sports during secondary school and thereafter, indicating limited participation in specific social activities with peers. Social withdrawal due to shame and fear of bullying by peers in relation to constipation and fecal incontinence could be one explanation. In one of our own studies on disease related quality of life, we found that 50% children with constipation reported shame about their fecal incontinence and 20% reported being bullied (submitted). In addition, parental concern about peer rejection of their child due to fecal incontinence while playing with friends, may also have led to less stimulation to participate in social activities. On the other hand, the ability to become a member of a sports club may be limited by financial means given the lower socioeconomic status of our patients’ cohort.
Supporting our findings, earlier observations reported that children with fecal incontinence show mainly internalizing behavioral problems such as social withdrawal and lower self-esteem. Indeed, it has been recognized that interaction with peers is of importance for the child’s development of self-competence and self-esteem through friendships and comparisons. Furthermore, a previous study on quality of life in children and adolescents with organic causes of constipation and/or fecal incontinence, i.e. Hirschsprung’s disease and anorectal malformations, showed that children with high athletic competencies improved more in disease-specific functioning and self-esteem over time than their less athletic peers. This may very well be true for children with functional defecation problems. Therefore, we suggest that professional caretakers should specifically encourage participation in athletic activities in children and adolescents with constipation to promote bowel peristalsis and to encourage peer-activities.

The fact that especially young adults experiencing fecal incontinence, both as child and adolescent, reported delayed autonomy and social development, while this was not found for adults without a history of fecal incontinence or those without fecal incontinence after the age of 12 years, suggests that still experiencing fecal incontinence as adolescent has major impact. With respect to autonomy development, one could hypothesize that longstanding fecal incontinence unresponsive to medical or behavioral interventions results in frustration, anger and denial of the problems. Consequently, these adolescents are not able to take their own responsibility for their primary need to defecate. Furthermore, it is our daily clinical experience that parents often report to play an important role in reminding their child to regular toileting and to clean up their dirty underwear, even during adolescence. This could indicate that these parents pamper their children instead of stimulating them to acquire more independence. With regard to social development, adolescents in general are going through insecurities about their developing body. Feelings of shame or frustration caused by fecal incontinence could negatively influence self-esteem and social competence even more.

Surprisingly, however, psychosexual development was neither delayed in our total study population, nor in those young adults with ongoing fecal incontinence during adolescence. This is in contrast to findings in patients grown up with anorectal malformations and Hirschsprung’s disease. We speculate that this difference could at least partly be explained by the prevalence of other congenital malformations or a stoma in these patients with congenital bowel disease, which is not the case in children with functional constipation.

With regard to socio-demographic outcome, the percentage of low educational level was almost twice as high in adults grown up with functional constipation.
than their peers, while unemployment was more than five times higher in this
group of patients. Low educational level subsequently resulted in a higher
unemployment rate: 27.8% compared to 6.3% in middle to high educated
adults. Lower educational level found in parents of these young adults most
likely correlates with lower educational level in their children. In fact, our study
population showed an even lower level than their parents, who only differed
in middle and high educational level with parents of the reference group.
Conflicting data exist with respect to socioeconomic factors and its relation
with functional constipation in children 22, 23. In adults however, several studies
have shown that the presence of constipation is related to both lower income
and lower educational levels 24-26. Risk factors such as different lifestyle and
dietary habits, or increase social stress might be responsible for the higher
prevalence of functional gastrointestinal disorders among the disadvantaged
classes 24, 25. On the other hand, we do not know whether loss to follow up
may have influenced our data. Possibly adults who no longer lived with their
parents or who worked were not found or did not respond.
Some limitations of this study need to be addressed. Firstly, only a limited
number of variables for correction could be taken into account. In our
analyses, no correction was made for the difference in educational level
between parents of the study population and those of the reference group.
This may have resulted in an overestimation of the found differences in scale
scores on autonomy and social development. In the reference population, less
achievement of milestones correlated with lower parental educational level. As
the percentage of parents with low educational level in our study population
was similar to that of the reference group, overestimation is probably limited.
Secondly, this study had mainly an explorative nature, as this is the first
study addressing the relationship between the course of life and functional
constipation in young adults. Therefore, no correction for multiple testing was
done. Subsequently, phenomena’s may exist in our study population, but may
not apply to other study populations. Lastly, the differences found in this study
could be due to other medical factors than fecal incontinence, such as chronic
pain, or be influenced by psychosocial factors, such as coping mechanisms,
family functioning or interaction between children and parents. Future studies
should further evaluate the protective and risk factors for a delayed course of
life in children growing up with functional constipation in more detail.
In conclusion, clinicians treating children with chronic functional constipation
should stimulate children in their social interaction with peers and encourage
parents to stimulate their child’s independence, especially when fecal
incontinence continues into adolescence. The impact of lower socioeconomic
status in adults with a history of childhood constipation on course of life needs to be further evaluated.

Acknowledgements
The study was funded by the Dutch Digestive Diseases Foundation (MLDS, SWO 03-13).
REFERENCES


Course of life in adults with childhood constipation


Appendix chapter 4
<table>
<thead>
<tr>
<th>Study, Quality score (QS)</th>
<th>Study population</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
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<tbody>
<tr>
<td>Banasz-kiewicz et al., 2006 16</td>
<td>Inclusion: between 2-16 years of age with constipation (&lt;3 BMs per week for at least 12 weeks) Exclusion: Enteric neuromuscular, anatomic, or metabolic diseases N=84 Gender: M/F 36/48 Age (mean ±SD): 96.0 ± 41.5 mo; Duration: 71.9 ± 41.7 mo; Severity: 2.2± 0.6 BMs/week Setting: Paediatric gastroenterology department</td>
<td>Lactulose+LGG versus lactulose+ placebo</td>
<td>24 months Loss to FU: 6%,</td>
</tr>
<tr>
<td>De Lorijn et al., 2004 17</td>
<td>Inclusion: &gt;5 years of age with constipation (at least 2 of the following: &lt;3BM/week; &gt;1 episode of encopresis/week; passing of very large stool every 7-30 days; palpable abdominal or rectal mass). Exclusion: Hirschsprung’s disease, spinal and anal anomalies, previous colon surgery, metabolic or renal abnormalities, mental retardation N=169 Gender: M/F: 109/60; Age: median (25th-75th centiles) 8.4 yrs (7.0-10.5); Onset: median age 3.5 yrs (1.0-4.0) Severity: median BMs/wk 2.0 (1.0-2.0); median encopresis freq/ wk: 10.0 (5.5-21.0) Setting: Paediatric gastroenterology department</td>
<td>High fibre diet, toilet advice, laxatives (lactulose, desimpaction with enemas) and biofeedback training or anorectal manometry.</td>
<td>12 months Loss to FU: no information</td>
</tr>
<tr>
<td>Elshimy et al., 2000 18</td>
<td>Inclusion: &lt;5 years of age with constipation (unspecified) Exclusion: no criteria presented N=42 Gender not presented Age mean 21months (range 1-58); Duration: 12.5 months (range 1-48) Severity: not presented Setting: General paediatric department</td>
<td>Laxatives, advice of generous intake of dietary fibre and fluids</td>
<td>18 months Loss to FU: 2.2%</td>
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</table>
Table 2. Study characteristics

<table>
<thead>
<tr>
<th>Study, Quality score (QS)</th>
<th>Study population</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Recovery definition</th>
<th>Prognostic factors</th>
<th>Results</th>
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<tr>
<td>Banasz-kiewicz et al., 2006</td>
<td>QS 8</td>
<td>Inclusion: between 2-16 years of age with constipation (&lt;3 BMs per week for at least 12 weeks) Exclusion: Enteric neuromuscular, anatomic, or metabolic diseases</td>
<td>Lactulose+LGG versus lactulose+ placebo</td>
<td>24 months</td>
<td>None presented</td>
<td></td>
</tr>
<tr>
<td>De Lorijn et al., 2004</td>
<td>QS 10</td>
<td>Inclusion: &gt;5 years of age with constipation (at least 2 of the following: &lt;3BMs/week; &gt;1 episode of encopresis/week; passing of very large stool every 7-30 days; palpable abdominal or rectal mass). Exclusion: Hirschsprung’s disease, spinal and anal anomalies, previous colon surgery, netabolic or renal abnormalities, mental retardation</td>
<td>High fibre diet, toilet advice, laxatives (lactulose, desimpaction with enemas) and biofeedback training or anorectal manometry.</td>
<td>12 months</td>
<td>None presented</td>
<td></td>
</tr>
<tr>
<td>Elshimy et al., 2000</td>
<td>QS 4</td>
<td>Inclusion: &lt;5 years of age with constipation (unspecified) Exclusion: no criteria presented</td>
<td>Laxatives, advice of generous intake of dietary fibre and fluids</td>
<td>18 months</td>
<td>None presented</td>
<td></td>
</tr>
<tr>
<td>Study, quality score (QS)</td>
<td>Study population</td>
<td>Treatment</td>
<td>Follow-up</td>
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<tr>
<td>Loening-Baucke 198722</td>
<td>Inclusion: children with encopresis and constipation (unspecified) for &gt;1 yr and presence of a large amount of stools in the rectum. Exclusion: age &lt;5 yrs, previous colon surgery, hypothyroidism, Hirschsprung's disease, mental deficiency, chronic debilitating disease. N=25. Gender: M/F 19/6; Age mean 9.9 yrs (range 5.8-15.4); Duration &gt;1 yr. Severity: encopresis freq. range 3-10/day Setting: General paediatric department</td>
<td>Disimpaction in case of enormous fecal retention, milk of magnesia, high fibre diet, instructions in bowel training techniques</td>
<td>9-16 months Loss to FU: 0%</td>
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<tr>
<td>Loening-Baucke 198923</td>
<td>Inclusion: children with chronic constipation (unspecified) and overflow incontinence Exclusion: age &lt;5 yrs, hypothyroidism, Hirschsprung's disease, mental deficiency, chronic debilitating disease, previous colon surgery. N=104. Gender: M/F:69/28. Age mean 9.0 years (±2.4). Duration: not presented, Severity: mean soiling freq: 15/wk, palpable fecal mass in the abdomen: 45% Setting: General paediatric department</td>
<td>Disimpaction in case of enormous fecal retention, milk of magnesia, high fibre diet, instructions in bowel training techniques</td>
<td>12 months Loss to FU: 6.7%</td>
<td></td>
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<tr>
<td>Loening-Baucke 199324</td>
<td>Inclusion: children £4 yrs with constipation (≤3 BMs/wk or painful defecation, or rectal impaction, or an abdominal fecal mass. Exclusion: hypotonia, cerebral palsy, severe mental retardation, Hirschsprung's disease, anal atresia, or spinal disease N=174. Gender: M/F: 87/87. Age mean 2.2 (±1.3) yrs; Duration: mean age of onset: 11 (±13) months; Severity: &lt;1 BM/wk: 13%, ≤ 1 BM/wk: 32%, &lt;3 BMs/wk: 58% Setting: General paediatric department</td>
<td>Disimpaction (phosphate enema), education, prevention by daily laxative use (milk of magnesia) and an increase of dietary fibre, and scheduled toilet sittings</td>
<td>mean 6.9 (±2.7) yrs. Loss to FU: 48.3%</td>
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</tr>
<tr>
<td>Recovery definition</td>
<td>Recovery at end of follow-up</td>
<td>Prognostic factors</td>
<td>Results</td>
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<tr>
<td>≥3 BM/wk, ≤2 smear/month or no soiling at all, while off laxatives for at least a month</td>
<td>12 month recovery rate: 36%</td>
<td>1) presence of a palpable abdominal fecal mass 2) ability to relax external sphincter 3) ability to defecate rectal balloon 4) age at presentation 5) time of onset of constipation/encopresis 6) soiling frequency 7) history of severe abdominal pain</td>
<td>1) P&lt;0.0001 2) Recovery 70%(yes) vs. 13% (no) 3) Recovery 64%(yes) vs. 14% (no) 4-7) No association measures presented; no statistical significant association.</td>
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</tr>
<tr>
<td>≥3 BM/wk, ≤2 smear/month or no soiling at all, while off laxatives for at least a month</td>
<td>12 month recovery rate: 43%</td>
<td>1) mean soiling freq/wk (recovered vs non-recovered) 2) presence of a palpable abdominal fecal mass 3) inability to defecate rectal balloons 4) abnormal contraction of the external anal sphincter 5) gender 6) age at presentation 7) time of onset of constipation and soiling 8) defecation frequency 9) history of severe abdominal pain 10) nighttime urinary incontinence 11) previous urinary tract infection</td>
<td>1) 10 vs 18, p&lt;0.002 2) 26% vs 62%, p&lt;0.0006 3) in relation to treatment failure (p&lt;0.04) 4) in relation to treatment failure (p&lt;0.01) 5-11) No association measures presented; no statistical significant association.</td>
<td></td>
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<tr>
<td>≥3 BM per week, no soiling, and receiving no drugs or treatment</td>
<td>12 month recovery rate: 63%</td>
<td>1) gender 2) age at presentation 3) time of onset of constipation 4) defecation frequency 5) stool withholding 6) urinary tract infection 7) abdominal or rectal mass</td>
<td>1-7) No association measures presented; no statistical significant association</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Study, quality score (QS)</td>
<td>Study population</td>
<td>Treatment</td>
<td>Follow-up</td>
<td></td>
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</tbody>
</table>
| Loening-Baucke 199626 | Inclusion: children with constipation (unspecified) and encopresis  
Exclusion: Hirschsprung disease, hypothyroidism, mental deficiency, chronic debilitating diseases or neurologic abnormalities, and previous surgery of the colon  
N=232.  
Gender: M/F:176/56;  
Age mean 9±3 yrs;  
Duration: not presented  
Severity: not presented  
Setting: General paediatric department | Disimpaction, education, prevention by daily laxative use and an increase of dietary fibre, and scheduled toilet sittings. In case of anismus: biofeedback | 12 months. Loss to FU: 40% |
| Miele et al., 200426 | Inclusion: children with a FGID according to the Rome II criteria  
Exclusion: no criteria presented  
N=66.  
Gender: M/F 30/36;  
Age mean 3.9±2.8 yrs,  
Duration: age at onset:2.1±1.8,  
Severity: not presented  
Setting: General paediatric department | Disimpaction, followed by maintenance therapy with an osmotic laxative and recommendations to increase dietary fibre | 12 months. Loss to FU: 29% |
| Polanco et al., 200427 | Inclusion: children with constipation (<3 BM/wk for at least 3 months with difficult and painful defecation).  
Exclusion: no criteria presented  
N=154  
Gender: M/F: 72/82;  
Age mean 6.3±3.33 yrs  
Duration: age of onset 2-4 yrs: 23.8%, onset >4 yrs: 39.5%,  
Severity: abdominal pain: 53.2%, palpable abdominal mass: 8.15%.  
Setting: Paediatric gastroenterology department | Toilet training, diet rich in fibre, maintenance medication if necessary | 6 months. Loss to FU: no information |
| Staiano et al., 199426 | Inclusion: children with constipation (unspecified) for at least 6 months  
Exclusion: hypoparathyroidism, hyperparathyroidismspinal and anal anomalies and mental retardation.  
N=103.  
Gender: M/F: 61/42.  
Age median 4.7 yrs (range 1.3-11.3),  
Duration: at least 6 months;  
Severity: median def.freq./wk 2 (range 1-4).  
Setting: not specified | Toilet training, high fibre diet, removal of impacted feces by enemas, microlax suppositories, or rectal infusion of saline, and high doses of lactulose for 3-5 days. Lactulose was continued for 3 months. | 5 yrs. Loss to FU: at 1 yr: 30%; At 5 yrs: 39.8% |
## Recovery definition and follow-up

<table>
<thead>
<tr>
<th>Recovery definition</th>
<th>Recovery at end of follow-up</th>
<th>Prognostic factors</th>
<th>Results</th>
</tr>
</thead>
</table>
| A) ≥3BM/wk and ≤2soiling episodes per month while off laxatives for at least one month  
B) ≥3BM/wk and ≤2soiling episodes per month, no abdominal pain, irrespective of laxative use | A) 41.7%  
B) 47.5%     | 1) ability to defecate a 100 ml rectal balloon  
2) secondary encopresis (medical history) | 1) OR 2.13 (95%CI 1.06-4.29), p<0.04  
2) OR 2.09 (95%CI 1.04-4.23), p<0.04 |

| unspecified | 70% | None presented |

| ≥3 BM/day | At 6 months: 98.4% | None presented |

| >4BM/wk and/or TGTT <33 hr After 5 year: 48% while off laxatives for at least a month | 1) history of constipation in the first year of life  
2) pos. family history  
3) presence of abdominal pain at 1 yr from diagnosis  
4) age of onset  
5) soiling frequency  
6) age at presentation  
7) presence of abdominal pain at presentation  
8) gender  
9) defecation frequency  
10) megarectum/ megacolon at diagnosis  
11) TGTT at diagnosis | Recovered vs non recovered (1-3):  
1) 33.3% vs 53.1% (p<0.05);  
2) 26.6% vs 40.6% (p<0.05);  
3) p<0.05 with persistence  
4) 3.0±2.9 vs 1.8±1.4 (p<0.05)  
5-11) no statistical significant association |
<table>
<thead>
<tr>
<th>Study, quality score (QS)</th>
<th>Study population</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van den Berg et al., 2005&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Inclusion: children with constipation (one of the following: &lt;3/BM/week; painful def; use of laxatives) in first year of life. Exclusion: organic causes of constipation such as gastrointestinal malformations, spinal abnormalities, cerebral palsy, Hirschsprung’s diseases. N=47 Gender: M/F: 28/19 Age median (25th-75th centiles) 3.5 months (2.0-13.5). Duration: median 3 (2-9.2) mo Severity: median 2 BM/week (0-7); Setting: Paediatric gastroenterology department</td>
<td>Elimination of fecal impaction with enemas (sodium docusate sorbitol or sodium lauryl sulfosuccinate) followed by oral laxatives (lactulose or PEG)</td>
<td>Median FU 20 months (range 6-52) Loss to FU: 11%.</td>
</tr>
<tr>
<td>van Ginkel et al., 2003&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Inclusion: children with constipation (≥ at least 2 of the following: &lt;3 BMs/week, ≥2 episodes of encopresis/week, periodic passage of very large amounts of stool at least one every 7-30 days, palpable abdominal or rectal mass) Exclusion: organic causes of constipation and children using drugs influencing gastrointestinal function other than laxatives N=418 Gender: M/F: 139/279 Age median (25th-75th centiles) 8 (6-10) yrs; Duration: period of symptoms before intake median 5 yrs + 5 mo Severity: median 2 (1-5.5) BMs/week; median encopresis freq/week: 2 (3-17) Setting: Paediatric gastroenterology department</td>
<td>Standard conventional treatment protocol (enemas, lactulose, high fibre diet, education). 297 children received additional treatment (biofeedback or anorectal manometry)</td>
<td>Median FU 5 yrs (range 1-8). Loss to FU at 1 yr: 4.5%</td>
</tr>
<tr>
<td>Martinez-Costa et al., 2005&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Inclusion: children &gt;4 yrs with chronic functional constipation (≥3 BM/week since the previous 2 months; voluminous or scybalous stools; pain or straining; ≥2 soiling episodes/week). Exclusion: organic causes of constipation such as encephalopathy, Hirschsprung’s disease etc. N=62 Gender M/F 25/37 Age median 6.1 yrs (range 1-14); Duration ≥2 months, Severity: encopresis 31%, faecal impaction 27% Setting: Paediatric gastroenterology department</td>
<td>Disimpaction and maintenance treatment (senna/mineral oil)</td>
<td>12 months. Loss to FU and...</td>
</tr>
</tbody>
</table>
## Study, quality score (QS)

<table>
<thead>
<tr>
<th>Recovery definition</th>
<th>Recovery at end of follow-up</th>
<th>Prognostic factors</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>at least 4 weeks with ≥3 BMs/wk, no pain during def and no laxative use</td>
<td>At 12 months off laxatives: 60% At 12 months with laxatives: 17%</td>
<td>1) &lt;2 months of treatment before presentation 2) &lt;3 months of symptoms before intake 3) gender 4) age of onset 5) def freq at presentation 6) prematurity at birth 7) delayed passage of meconium 8) pos fam history (standardized questionnaire)</td>
<td>1) RR 2.4 (95%CI 1.2-4.8) 2) RR 2.5 (95%CI 1.1-3.7) 3-8) no statistical significant association</td>
</tr>
<tr>
<td>at least 4 wks with ≥3 BM/wk with ≥2 encopresis episodes/month, no laxative use</td>
<td>-At 12 months off laxatives: 59% -At 12 months with laxatives: 24%</td>
<td>1) onset of complaints &gt;4 yrs (&lt;1 yr = ref) 2) difference of 7 encopresis episodes/wk at intake 3) duration of symptoms 4) pos fam history 5) -hard fecal bolus found on physical examination 6) male sex</td>
<td>1) RR for first succes: 1.55 (95%CI 1.11-2.15) 2) 0.87 (95%CI 0.80-0.94) 3-6) no statistical significant association</td>
</tr>
</tbody>
</table>

- Positive outcome: ≥3 BM/wk, no pain, <2 soiling episodes/month

After 6-12 months: 85%

None presented

None presented
Table 3. Prognostic factors (best evidence synthesis)

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Methodological quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>High</td>
</tr>
<tr>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Age at intake</td>
<td>Low</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
</tr>
<tr>
<td>Age of onset</td>
<td>High</td>
</tr>
<tr>
<td>Low</td>
<td></td>
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<tr>
<td>Positive family history for childhood constipation</td>
<td>High</td>
</tr>
<tr>
<td>Low</td>
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</tr>
<tr>
<td>&lt;3 months symptoms before presentation</td>
<td>High</td>
</tr>
<tr>
<td>&lt;2 months treatment before presentation</td>
<td>High</td>
</tr>
<tr>
<td>Premature birth</td>
<td>High</td>
</tr>
<tr>
<td>Delayed passage of meconium</td>
<td>High</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td></td>
</tr>
<tr>
<td>Defecation frequency</td>
<td>High</td>
</tr>
<tr>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Presence of fecal incontinence episodes</td>
<td>Low</td>
</tr>
<tr>
<td>Frequency of fecal incontinence episodes</td>
<td>High</td>
</tr>
<tr>
<td>Study Results</td>
<td>Association with recovery</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>17 OR 0.34 (0.16-0.70)</td>
<td>neg</td>
</tr>
<tr>
<td>31 no association measures presented</td>
<td>no</td>
</tr>
<tr>
<td>32 OR 1.08 (0.82-1.42)</td>
<td>no</td>
</tr>
<tr>
<td>23 no association measures presented</td>
<td>no</td>
</tr>
<tr>
<td>24 no association measures presented</td>
<td>no</td>
</tr>
<tr>
<td>29 OR 1.71 (0.62-4.77)</td>
<td>no</td>
</tr>
<tr>
<td>22 no association measures presented</td>
<td>no</td>
</tr>
<tr>
<td>23 no association measures presented</td>
<td>no</td>
</tr>
<tr>
<td>24 no association measures presented</td>
<td>no</td>
</tr>
<tr>
<td>29 recovered 11.1y±3.4 vs. non-recovered 10.3y±3.1 (p=0.34)</td>
<td>no</td>
</tr>
<tr>
<td>31 no association measures presented</td>
<td>no</td>
</tr>
<tr>
<td>32 &gt;4y (&lt;1y = ref): RR 1.55 (1.11-2.15)</td>
<td>pos</td>
</tr>
<tr>
<td>22 no association measures presented</td>
<td>no</td>
</tr>
<tr>
<td>23 no association measures presented</td>
<td>no</td>
</tr>
<tr>
<td>24 no association measures presented</td>
<td>no</td>
</tr>
<tr>
<td>29 recovered 3.0y±2.9 vs non-recovered 1.8y±1.4 (p&lt;0.05)</td>
<td>pos</td>
</tr>
<tr>
<td>31 no association measures presented</td>
<td>no</td>
</tr>
<tr>
<td>32 RR 1.14 (0.79-1.64)</td>
<td>no</td>
</tr>
<tr>
<td>29 recovered 26.6% vs non-recovered 40.6% (p&lt;0.05)</td>
<td>neg</td>
</tr>
<tr>
<td>31 no association measures presented</td>
<td>pos</td>
</tr>
<tr>
<td>31 no association measures presented</td>
<td>pos</td>
</tr>
<tr>
<td>31 no association measures presented</td>
<td>no</td>
</tr>
<tr>
<td>31 no association measures presented</td>
<td>no</td>
</tr>
<tr>
<td>17** ≥3/wk OR=1 (ref)</td>
<td>Strong evidence for no association</td>
</tr>
<tr>
<td>&gt;1-3/wk: 1.48 (0.54-4.08)</td>
<td></td>
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<tr>
<td>0-1/wk: 1.06 (0.40-2.80)</td>
<td>no</td>
</tr>
<tr>
<td>31 no association measures presented</td>
<td>no</td>
</tr>
<tr>
<td>23 recovered 5±4wk vs. non-recovered 4±5 (p=0.28)</td>
<td>no</td>
</tr>
<tr>
<td>24 no association measures presented</td>
<td>no</td>
</tr>
<tr>
<td>29 recovered 2.3±1.7/wk vs. non-recovered 1.9±1.8 (p=0.37)</td>
<td>no</td>
</tr>
<tr>
<td>25 OR 2.09 (1.04-4.23) (p&lt;0.04)</td>
<td>pos</td>
</tr>
<tr>
<td>29 recovered 6.6% vs. non-recovered 12.5%,</td>
<td>no</td>
</tr>
<tr>
<td>OR 1.81 (0.34-11.82)</td>
<td></td>
</tr>
<tr>
<td>17** no encopresis: OR=1 (ref); &lt;1/day: 0.58 (0.14-2.43)</td>
<td>no</td>
</tr>
<tr>
<td>1-2/day: 0.44 (0.11-1.68); ≥2/day: 0.44 (0.12-1.68)</td>
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<tr>
<td>Prognostic factor</td>
<td>Methodological quality</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Abdominal pain at presentation/ history of abdominal pain</td>
<td>Low</td>
</tr>
<tr>
<td>Production of large stools</td>
<td>High</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Low</td>
</tr>
<tr>
<td>Nighttime urinary incontinence</td>
<td>Low</td>
</tr>
<tr>
<td>Stool withholding</td>
<td>Low</td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
</tr>
<tr>
<td>Absence of a rectal or abdominal mass</td>
<td>High</td>
</tr>
<tr>
<td>Additional examination</td>
<td></td>
</tr>
<tr>
<td>Balloon defecation</td>
<td>Low</td>
</tr>
<tr>
<td>Relaxation of external sphincter</td>
<td>Low</td>
</tr>
<tr>
<td>CTT/TGTT</td>
<td>High</td>
</tr>
<tr>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Megarectum and/or megacolon at diagn</td>
<td>Low</td>
</tr>
</tbody>
</table>

*: not included in best evidence synthesis **: results summarized as `no`
<table>
<thead>
<tr>
<th>Study Results</th>
<th>Association with recovery</th>
<th>Best evidence synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>32 difference of 7 encopresis episodes/wk at intake: RR = 0.87 (0.80-0.94)</td>
<td>neg</td>
<td></td>
</tr>
<tr>
<td>22 no association measures presented</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>23 recovered 10/wk vs non-recovered 18/wk, p&lt;0.002</td>
<td>neg</td>
<td></td>
</tr>
<tr>
<td>22 no association measures presented</td>
<td>no</td>
<td>Limited evidence for no association</td>
</tr>
<tr>
<td>23 recovered 49% vs. non-recovered 44%, OR 1.22 (0.55-2.74)</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>29 no association measures presented</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>17 OR 1.09 (0.51-2.30)</td>
<td>no</td>
<td>Limited evidence for no association</td>
</tr>
<tr>
<td>23 OR 0.35 (0.09-1.27)</td>
<td>no</td>
<td>Insufficient</td>
</tr>
<tr>
<td>24 no association measures presented</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>23 no association measures presented</td>
<td>no</td>
<td>Insufficient</td>
</tr>
<tr>
<td>24 no association measures presented</td>
<td>no</td>
<td>Insufficient</td>
</tr>
<tr>
<td>17 Rectal mass: OR 3.39 (1.30-8.83)</td>
<td>pos</td>
<td>Conflicting</td>
</tr>
<tr>
<td>Abdominal mass: OR 1.23 (0.49-3.10)</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>32 Hard fecal bolus: RR 0.97 (0.74-1.28)</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>22* Presence of abdominal mass related to non recovery: p&lt;0.0001</td>
<td>neg</td>
<td></td>
</tr>
<tr>
<td>Abdominal mass: recovered 26% vs non-recovered 62%, p&lt;0.0006</td>
<td>neg</td>
<td></td>
</tr>
<tr>
<td>23 Abdominal / rectal mass: no association measures presented</td>
<td>neg</td>
<td></td>
</tr>
<tr>
<td>24 no association measures presented</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>22 ability to defecate at least 2/3 balloons: no association measures presented</td>
<td>pos</td>
<td>Insufficient</td>
</tr>
<tr>
<td>inability to defecate a 100ml balloon in ≤1 min related to treatment failure: p&lt;0.04</td>
<td>pos</td>
<td>Insufficient</td>
</tr>
<tr>
<td>23* ability to defecate balloon: OR 2.13 (1.06-4.29) (p&lt;0.04)</td>
<td>pos</td>
<td></td>
</tr>
<tr>
<td>25 no association measures presented</td>
<td>pos</td>
<td></td>
</tr>
<tr>
<td>22 ability to relax external sphincter: no association measures presented</td>
<td>pos</td>
<td>Insufficient</td>
</tr>
<tr>
<td>23* abnormal contraction of external sphincter related to treatment failure: p&lt;0.01</td>
<td>pos</td>
<td></td>
</tr>
<tr>
<td>17 CTT&gt;100 hrs: OR 0.31 (0.12-0.85)</td>
<td>neg</td>
<td>Limited evidence for negative association</td>
</tr>
<tr>
<td>29 TGTT (hrs) : recovered: 87.6±22.0 vs. non-recovered 89.3±19.9 (p=0.75)</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>29 recovered 53.3% vs non-recovered 62.5%</td>
<td>no</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>
Summary & Discussion
SUMMARY

Functional constipation in children is a challenging disorder, as the underlying pathophysiology is not fully understood and treatment is mainly based on empiricism rather than evidence. Long-term studies showed that a subgroup of patients is unresponsive to varying treatment strategies (e.g. education, dietary advice, laxatives, and behavioral recommendations). These children have persisting symptoms into adolescence or young adulthood. This thesis focused on new treatment modalities directed at possible underlying mechanisms which influence occurrence or persistence of functional constipation in children. Furthermore, prognosis and prognostic factors of childhood constipation were studied up to the adult age. Finally, this thesis aimed to improve insight in health-related quality of life and the course of life of children growing up with chronic complaints of constipation and fecal incontinence.

Part I – Clinical interventions for functional constipation

In Chapter 1 a randomized controlled trial is described that evaluated the effect of an infant formula with a high proportion of sn-2 palmitate, a mixture of prebiotic galacto-oligosaccharides and fructo-oligosaccharides and partially hydrolyzed whey protein on constipation in infants. It was demonstrated that the use of this modified infant formula compared to a standard formula led to softer stools in these infants, but not to a stronger increase in defecation frequency. Thus, infants with constipation who present with hard stools may benefit from a change from the standard formula to this modified formula as a first treatment step.

Retentive posturing or stool-withholding behavior is thought to play an important role in development and/or persistence of childhood constipation. Hard stools and painful defecation may lead to fear and avoidance of defecation in children and vice versa; a vicious circle that can be described as learned behavior. A specifically behavioral therapy, based on cognitive-behavioral theories, was developed by pediatric psychologists for constipated children. In Chapter 2, the results are presented of a large randomized controlled trial, which showed that behavioral therapy in combination with laxatives has no advantage over conventional treatment in treating childhood constipation. However, more than one-third of the participating children exhibited general behavior problems. Behavioral therapy was shown to be superior to conventional treatment in addressing these behavior problems in constipated children. Therefore, when behavioral problems are present in children with constipation, behavioral
therapy or referral to mental health services for treatment of these problems should be considered.

In Chapter 3 we described a randomized controlled trial in which we compared clinical effectiveness of maintenance treatment with rectal enemas in addition to oral laxatives to treatment with oral laxatives alone in severely constipated children. Although application of rectal enemas on a regular basis was well tolerated, it did not result in higher success rates compared to treatment with oral laxatives alone. Therefore, there is no role for rectal enemas in the maintenance treatment of functional constipation and they should only be used for initial disimpaction.

**Part II – Prognosis of functional constipation**

In Part II of the thesis we focused on the clinical course of childhood constipation and prognostic factors for successful outcome.

Chapter 4 is a systematic review of the literature regarding current knowledge on prognosis and prognostic factors of childhood constipation. This literature review showed that recovery rates of functional constipation in children vary widely, caused by the fact that the definitions, patients’ populations and outcome measurements used were heterogeneously. Despite this variation, overall 6 to 12 month recovery rate extracted from the currently available data is approximately 60%. High level of evidence was found that defecation frequency and positive family history for functional gastrointestinal disorders is not related with prognosis. For other prognostic factors identified, e.g. gender, age at onset, duration of symptoms, fecal incontinence frequency or disturbed anorectal parameters, insufficient or low level of evidence was found, making it impossible to draw reliable conclusions about their relation with clinical outcome.

A long-term prospective follow-up of 401 children with functional constipation is described in Chapter 5. This study showed that after 10 years follow-up almost all patients achieved good clinical outcome at least once, as the cumulative percentage of initial success was 94% for girls and 92% for boys. However, relapse after initial success was common, occurring in approximately half of the children within 10 years of follow-up. Furthermore, approximately 25% of children with functional constipation have persisting symptoms into adulthood. Poor clinical outcome at adult age was correlated with later age of onset, longer delay between age of onset and first presentation to our pediatric gastrointestinal outpatient clinic, and lower defecation frequency at first presentation. Referral to a specialized clinic should be considered at an early stage for children unresponsive to first line treatment.
Part III – Health-related quality of life and chronic constipation

In the last part of this thesis health-related quality of life (HRQoL) in both children with long-term constipation and adults with persistence of constipation was presented. In adults with a history of childhood constipation, the course of life was evaluated to gain insight whether growing up with chronic symptoms of constipation influences achievement of developmental tasks and milestones.

In Chapter 6 we describe HRQoL as measured with a disease-specific questionnaire, the Dutch Defecation list (DDL). Children with frequent episodes of constipation-associated fecal incontinence reported lower HRQoL with respect to emotional and social functioning. The majority of children reported relatively more emotional concerns than social consequences. Yet, one needs to be alert to bullying by peers, which was reported in 23% of these children. A disease-specific HRQoL questionnaire is a valuable tool to recognize and address the possible impact of chronic constipation on children. However, further adjustment to the DDL with thorough evaluation of its validity is needed.

Health-related quality of life (HRQoL) in adults with persistence of childhood constipation was presented in Chapter 7. Unsuccessful clinical outcome at adult age was associated with lower HRQoL. Compared to healthy controls, these adults reported worse general health perception and bodily pain. This seems in line with the finding that adults with unsuccessful clinical outcome complained approximately twice more often of pain, i.e. painful defecation and abdominal pain, than those adults who achieved successful clinical outcome. Social consequences, measured with a study-specific questionnaire, as result of persistence of symptoms were reported in one-fifth of adults with unsuccessful clinical outcome. Further quantification of the burden of childhood constipation continuing into adulthood is needed to determine the best course for prevention and treatment strategies.

In Chapter 8, the course of life of young adults grown up with functional constipation is described. This study assessed development during childhood and adolescence with regard to achievement of autonomy, psycho-sexual and social milestones, also in relation to the period when fecal incontinence was experienced. It was found that these adults reported a delayed course of life compared to that of the reference group, as they achieved fewer milestones on autonomy and social development than their peers. A delayed course of life was especially found in the subgroup of adults with fecal incontinence up to a maximum of 18 years of age, but not in adults who never experienced fecal incontinence or those without fecal incontinence after the age of 12. Based on these findings, clinicians treating children with chronic functional constipation
should stimulate children in their social interaction with peers and encourage parents to stimulate their child’s independence, especially when fecal incontinence continues into adolescence. With respect to socio-demographic outcomes, our study population showed lower educational level than the reference group, while unemployment rate was higher. The relationship between course of life and lower socio-economic status in patients with childhood constipation persisting into adulthood needs to be further evaluated.

Discussion & Future perspectives

As described in this thesis, it is still necessary to improve treatment of functional constipation, as with currently available therapies a subgroup of children fails to achieve successful clinical outcome. Some children suffer from constipation for years and their symptoms may even persist into adulthood. Development of new treatment strategies is challenging for several reasons. First of all, diagnosis of functional constipation in children is based on a complex of clinical symptoms, while even today no standard diagnostic tools are available. Due to the lack of insight in underlying pathophysiology, treatments are mainly based on empiricism rather than rationale. An important first step to improve both insight in pathophysiology and management of functional disorders is worldwide consensus on the definition of functional gastrointestinal disorders. A group of experts in the field of pediatric gastroenterology has recently reached international consensus of the criteria for these disorders in children, as formulated in the Rome III-criteria\(^1,2\). Usage of these criteria should facilitate comparison of research data and stimulate collaboration in this field. However, worldwide implementation still needs to be encouraged. Nonetheless, even when using these criteria, one must be aware of the fact that children with functional constipation may encompass a heterogeneous group of patients. This heterogeneity will complicate the development of effective treatment strategies. For instance, one could hypothesize that children with constipation, presenting with fecal incontinence may differ from those without fecal incontinence. Differences in clinical presentation may be correlated with different underlying physiologic abnormalities. However, one could also hypothesize that differences in clinical presentation between patients could partly be explained by differences in psychosocial factors (e.g. behavioral, family and environmental aspects). These factors may also play a role in the patient’s response to treatment. Whether children with functional constipation should be further divided into subclasses, based on their clinical presentation,
as done in adult patients with functional gastrointestinal disorders (e.g. irritable bowel syndrome) needs to be further investigated.

In this thesis, different treatment strategies based on current hypotheses of underlying mechanisms either causing or maintaining constipation in children were tested. In infants, onset of constipation is often associated with changing from breast feeding to infant formulas or the introduction of solid food. Differences in composition between different types of infant feedings in relation to maturation of the gastrointestinal tract are thought to play an important role in the commencement of constipation at this young age. To date, beneficial effects and safety of modified infant formulas mimicking the composition of breast milk still need to be further investigated in larger well designed randomized clinical trials. However, many of these infants formulas are already promoted on the market with specific health claims saying that these products promote a normal intestinal function and strengthen the immune system. Nevertheless, these products should be evaluated more thoroughly, not only for safety but also for their treatment efficacy. Similarly, the proclaimed gastrointestinal (beneficial) effects and safety of commercially available products with added pre- or probiotics for older children need to be verified as well.

In toddlers and young children, stool withholding behavior is regarded as one of the most important factors influencing both onset and persistence of functional constipation. Disappointingly, our protocolized behavioral therapy, specially developed for treatment of children with constipation, was found to be no more successful than conventional treatment. Although, behavioral problems in general were common in children with constipation, it remains the question whether these behavior problems are a primary or secondary problem. Therefore, screening for behavior problems in children with constipation may be useful in order to gain insight in coexisting behavioral factors, that may influence response and compliance to the treatment of constipation. Future research should evaluate whether children with specific behavior problems respond better to a specialized behavioral approach than to current conventional treatment.

Another subgroup within the group of children with constipation seems to be those children with severe constipation unresponsive to medical or behavioral treatment. More intensive laxative treatment was not found to improve clinical outcome of severely constipated children. In the literature, neuropathy or muscular dysmotilities are thought to be underlying causes of severe constipation. Colonic manometry has been proposed as a promising diagnostic tool to evaluate the motility of the entire colon. Based on
abnormalities in colon motility found with colonic manometry, it was thought to be possible to discriminate between neuropathy and myopathy. Yet, a recent study was unable to classify specific manometric findings as reflective of myopathic or neuropathic abnormalities. Further studies are needed to determine whether abnormal colonic manometry findings correlated with histopathological studies, in order to distinguish between these two entities.

Besides colonic peristalsis, the colon plays an important role in absorption of water and electrolytes. Alterations in water absorption in the colon may lead to a change in stool consistency and motility, subsequently causing severe constipation. Chloride channels are described to play an important role in the process of water and electrolyte excretion and absorption. Stimulation of chloride secretion induces the passive movement of sodium and water into the intestinal lumen, yielding a net increase in isotonic fluid, which results in improved intestinal motility. Recent studies in adults with constipation showed that a type-2 chloride channel activator was an effective treatment of constipation. Studies on the function of chloride channels in constipated children are currently in progress in our motility unit and will hopefully enhance our understanding and treatment of constipation.

Besides development of new treatment strategies, this thesis focused on gaining better insight in the prognosis of constipation. Knowledge on factors influencing the clinical course of functional constipation in children is important to enable general practitioners and paediatricians to give accurate patient information, to weigh treatment strategies and identify children with a high-risk for unfavourable outcome. It was found that data from previous literature was hardly conclusive on prognosis and predictive prognostic factors. This was mainly due to heterogeneity and poor methodological quality of the few studies published on prognosis of childhood constipation.

In general, functional constipation is often regarded as a mild disorder. From our long-term follow-up data, however, it became clear that functional constipation is not a self-limiting entity. The fact that a substantial group continues to experience problems at adult age is worrying. Lower health-related quality of life and hampered social and autonomy development in children growing up with long-lasting symptoms of constipation and fecal incontinence indicate that the impact of functional constipation reaches further than the gut. This subgroup of children with continuing symptoms of constipation is at risk for achieving less developmental milestones and experiencing lower health related quality of life both as child and adult. Clinicians treating children with chronic functional constipation need to address these possible negative psychosocial consequences during treatment. Future research should on the
one hand focus on how to recognize these ‘high-risk’ children at an early stage and on the other hand on development of accurate preventive strategies.

Research in the field of functional childhood constipation remains exciting and challenging as multiple aspects of this disorder still need to be elucidated and important advances still need to be made. It is essential that the definitions on functional gastrointestinal disorders, as formulated through international consensus, are implemented worldwide. Adequate insight in the pathophysiology underlying childhood constipation and fecal incontinence is still lacking. Validated diagnostic tools are essential for evaluation of the problem and proper risk assessment. Furthermore, new effective treatment strategies should be devised, addressing both the symptoms of constipation and its negative psychosocial consequences. These challenging developments may eventually lead to a significant improvement of quality of life and overall prognosis.

REFERENCES


Samenvatting & Discussie
SAMENVATTING

Obstipatie (verstopping) bij kinderen wordt in de ruime meerderheid (90-95%) geclassificeerd als functionele obstipatie, omdat er geen duidelijke onderliggende oorzaak aanwijsbaar is. Hierdoor is de behandeling van kinderen met functionele obstipatie vooral gericht op symptomen (o.a. lage ontlastingsfrequentie, incontinentie van ontlasting, buikpijn) zonder duidelijke wetenschappelijke basis. Onderzoeken die kinderen met obstipatie over langere tijd vervolgd hebben, laten zien dat een subgroep van kinderen (±30%) niet van de klachten afkomt ondanks verschillende behandelstrategieën (voorlichting, voedingsadviezen, laxeermiddelen en een gedragsmatige aanpak). Deze kinderen houden klachten van obstipatie als adolescent en soms zelfs op volwassen leeftijd. In dit proefschrift worden nieuwe behandelingsmogelijkheden voor kinderen met obstipatie onderzocht. Ook wordt er gekeken hoe het met de klachten van obstipatie staat naarmate kinderen ouder worden en uiteindelijk de volwassen leeftijd bereiken. Mogelijk kunnen demografische en specifiek medische kenmerken voorspellen welke kinderen uiteindelijk geen klachten van obstipatie meer zullen hebben. Tot slot, proberen we te achterhalen of de kwaliteit van leven en de levensloop van kinderen beïnvloed worden door het opgroeien met langdurige klachten van obstipatie.

Deel I – Klinische behandelingen van functionele obstipatie

In hoofdstuk 1 onderzochten we in baby’s met obstipatie het effect van een aangepaste flesvoeding, waaraan zowel een hoog percentage sn-2 palmitinezuur, als een prebiotica-mix en gedeeltelijk gehydrolyseerd wei-eiwitten toegevoegd was. Onze gegevens laten zien dat baby’s met obstipatie, die deze aangepaste flesvoeding kregen, zachtere ontlasting hadden dan baby’s die standaard flesvoeding kregen. Echter de defecatie (ontlasting) frequentie was evenveel toegenomen in de beide groepen. Alleen baby’s met obstipatie en tevens last van harde ontlasting lijken baat te hebben bij deze aangepaste flesvoeding. Wisseling van standaard flesvoeding naar deze aangepaste flesvoeding zou dan een eerste behandelstap kunnen zijn, in plaats van het geven van laxeermiddelen. Gedragsmatige veranderingen, zoals het ophouden van ontlasting, kunnen een rol spelen in het ontstaan en aanhouden van obstipatie in kinderen. Doordat kinderen bij het voelen van aandrang bewust dan wel onbewust de ontlasting tegenhouden, worden de intervallen tussen het moment van defecatie langer. Als gevolg hiervan wordt de ontlasting harder en hebben
Deze kinderen pijnlijke ontlasting, hetgeen weer een reden kan zijn om de ontlasting op te houden. Deze vicieuze cirkel kan worden beschreven als aangeleerd gedrag. Gespecialiseerde kinderpsychologen hebben daarom een specifieke gedragstherapie, gebaseerd op cognitieve gedragstheorieën, ontwikkeld voor kinderen met obstipatie. In hoofdstuk 2 hebben we bekeken of kinderen met obstipatie met behulp van deze gedragstherapie, in combinatie met het toedienen van laxeermiddelen, beter van hun klachten genezen dan wanneer ze volgens de standaardbehandeling (laxeren, toilettraining en beloningssysteem) bij de arts behandeld worden. Uit dit onderzoek bleek dat deze specifieke gedragstherapie niet succesvoller was dan de standaard behandeling van geconstipeerde kinderen. Een behandeling bij een arts met voldoende kennis op het gebied van obstipatie bij kinderen is dus nog steeds de eerste keus. Alleen bij kinderen die naast hun obstipatieklachten ook algemene gedragsproblemen laten zien, zou doorverwijzing naar de psycholoog voor behandeling van deze gedragsproblemen moeten worden overwogen.

Een subgroep van kinderen met obstipatie houdt jarenlang klachten ondanks behandeling bestaande uit dieetadviezen, gedragsinterventies en het gebruiken van laxeermiddelen. Hoofdstuk 3 beschrijft de resultaten van het regelmatig toedienen van rectale klysma’s in aanvulling op orale laxeermiddelen. Kinderen met ernstige en langdurige klachten van obstipatie bereikten ook met deze intensieve behandeling gedurende 1 jaar niet vaker succes dan wanneer ze alleen de orale laxeermiddelen kregen. Rectale klysma’s hebben dan ook alleen maar een rol als kortdurende behandeling wanneer er sprake is van ernstige ophoping van ontlasting in de endeldarm, en niet als onderhoudsbehandeling.

Deel II – Prognose van functionele obstipatie

Voor alle betrokkenen, zowel het kind en de ouders als de behandelend arts, is het belangrijk om inzicht te verkrijgen betreffende de prognose van obstipatie op de kinderleeftijd. Tevens is het van belang te weten welke factoren een succesvolle uitkomst mogelijk kunnen voorspellen. Hoofdstuk 4 is een literatuuronderzoek, waarin de huidige inzichten in enerzijds de prognose van obstipatie op de kinderleeftijd en anderzijds de factoren die hier mogelijk op van invloed zijn, worden beschreven. Dit onderzoek liet zien dat het succes percentage van kinderen met obstipatie, die 6 tot 12 maanden vervolgd zijn, gemiddeld 60% is. Echter de verschillende studies rapporteren zeer uiteenlopende succes percentages, variërend van 36.0% tot 98.4%. Deze grote variatie in het succes percentage kan waarschijnlijk verklaard worden doordat in de studies verschillende definities voor zowel obstipatie als succes gebruikt werden en
door de onderlinge verschillen tussen de onderzochte patiëntengroepen. Uit studies van hoge wetenschappelijke kwaliteit kon geconcludeerd worden dat de defecatie frequentie bij presentatie en het voorkomen van functionele darmaandoeningen binnen de familie geen voorspellende waarde hadden voor de prognose. Onvoldoende of tegenstrijdig bewijs werd gevonden om te kunnen zeggen of andere factoren, zoals geslacht, leeftijd bij begin van de klachten, duur van de klachten, frequentie van incontinentie voor ontlasting of gestoorde functie van de endeldarm en/of de kringspier, van invloed zijn op de uitkomst.

In hoofdstuk 5 worden de resultaten van een langdurig follow-up onderzoek in een cohort van 401 kinderen met obstipatie beschreven. Na 10 jaar follow-up werd gezien dat de meeste kinderen (94% van de meisjes en 92% van de jongens) in elk geval één periode klachtenvrij zijn geweest. Ongeveer de helft van deze kinderen heeft echter wel weer een terugval gehad in die periode van 10 jaar. Tijdens de follow-up periode bereikten in totaal 302 patiënten de volwassen leeftijd en hiervan rapporteerde een kwart van de patiënten nog steeds obstipatie. Het persisteren van obstipatie tot op volwassen leeftijd werd geassocieerd met 3 klinische kenmerken: (1) een latere leeftijd bij het begin van de klachten; (2) een langere tijd tussen het begin van de klachten en het eerste bezoek aan onze gespecialiseerde polikliniek ("de poeppoli"); (3) een lagere defecatie frequentie bij het eerste bezoek aan de poeppoli. Bij kinderen die niet goed reageren op behandeling in de eerste lijn, zou dus in een vroeg stadium een verwijzing moeten worden overwogen naar een polikliniek, die gespecialiseerd in de behandeling van functionele darmproblemen bij kinderen.

Deel III – Ziektegerelateerde kwaliteit van leven en chronische obstipatie

In het laatste deel van dit proefschrift wordt ziektegerelateerde kwaliteit van leven van zowel kinderen met chronische obstipatie als van volwassenen met aanhoudende obstipatie vanaf de kinderleeftijd beschreven. Ook werd bij volwassenen, die zijn opgegroeid met langdurige klachten van obstipatie, de levensloop onderzocht.

Voor het meten van kwaliteit van leven bij kinderen met obstipatie en/of incontinentie voor ontlasting is een speciale vragenlijst ontwikkeld: de Nederlandse Defecatie Lijst. In hoofdstuk 6 werd met behulp van deze vragenlijst gekeken of het hebben van obstipatie van invloed is op de kwaliteit van leven bij deze kinderen. Kinderen die regelmatig last hebben van fecale incontinentie (incontinentie van ontlasting) gaven aan een lagere kwaliteit van
leven te hebben op het gebied van emotioneel en sociaal functioneren. Kinderen met deze klachten gaven aan zich vooral veel zorgen te maken met betrekking tot hun klachten van obstipatie en fecale incontinentie. Sociale consequenties (minder vrienden, niet mee kunnen doen aan activiteiten op school of na school) werden minder vaak genoemd. Echter, 23% van de kinderen vermeldde dat ze naar aanleiding van hun klachten werden gepest door leeftijdgenoten. Om verder inzicht te krijgen hoe chronische klachten van obstipatie de kwaliteit van leven van deze kinderen beïnvloeden, is het belangrijk dat deze vragenlijst in de toekomst nog verder ontwikkeld wordt. Tevens zal de betrouwbaarheid van het gebruik verder getest moeten worden.

**Hoofdstuk 7** geeft een beschrijving van de ziektegerelateerde kwaliteit van leven van jong volwassenen met vanaf de kinderleeftijd aanhoudende klachten van obstipatie. Deze volwassenen gaven aan een lagere kwaliteit van leven te hebben dan gezonde leeftijdgenoten. In het bijzondere vermeldden deze volwassenen dat deze lagere kwaliteit van leven in verband stond met lichamelijke pijnklachten en een slechtere beleving van hun algemene gezondheid. Deze volwassenen hadden ook bijna twee keer zo vaak klachten van pijn, zoals pijnlijke defecatie en buikpijn, dan de volwassenen die genezen waren van hun obstipatieklachten op de kinderleeftijd. Een op de vijf volwassenen met aanhoudende obstipatieklachten gaf aan dat deze klachten invloed hadden op hun sociale contacten. In de toekomst is het nodig om nog meer inzicht te krijgen in de relatie tussen aanhoudende obstipatieklachten en de kwaliteit van leven bij volwassenen. Dit is van belang voor het identificeren van aanknopingspunten om met behulp van preventief beleid of aanpassingen van de huidige behandelingsmogelijkheden de kwaliteit van leven te verbeteren.

Het begrip levensloop staat voor het volbrengen van leeftijdsspecifieke ontwikkelingstaken en het behalen van ontwikkelingsmijlpalen. Op dit proces zijn zowel biologische ontwikkeling, omgevingsfactoren en persoonlijke keuzen van invloed. In **Hoofdstuk 8** wordt de levensloop beschreven van jong volwassenen, die zijn opgegroeid met langdurige klachten van obstipatie. In het bijzonder werd onderzocht of de levensloop van deze jong volwassenen beïnvloed is door het hebben van fecale incontinentie. De jong volwassenen met klachten van obstipatie hadden inderdaad een vertraagde levensloop in vergelijking tot een referentiegroep van leeftijdsgenoten. Onze patiëntengroep bereikte minder ontwikkelingsmijlpalen op het gebied van autonomie en sociale ontwikkeling. Met name die jong volwassenen die zowel last hadden van fecale incontinentie op jongere leeftijd (tussen 6-12 jaar) als gedurende de puberteit (>12 jaar) rapporteerde een vertraagde levensloop. Dit werd niet gevonden voor geconstipeerde kinderen die nooit klachten van fecale incontinentie hadden of de kinderen die geen fecale incontinentie meer
hadden in de puberteit. Dit betekent dat de behandelend arts zich met name bij adolescenten met obstipatie en fecale incontinentie er van bewust moet zijn dat sociale interactie met leeftijdgenoten gestimuleerd moet worden. Ook ouders moeten ertoe aangezet worden om de onafhankelijkheid van hun kind te stimuleren. De sociocultuurale uitkomst van onze studiepopulatie liet zien dat in de groep van jong volwassenen met chronische klachten van obstipatie op de kinderleeftijd het opleidingsniveau lager en werkloosheid percentage hoger was. Hoe de relatie ligt tussen de levensloop en de lagere sociocultuurale status van jong volwassenen die zijn opgegroeid met chronische klachten van obstipatie zal verder moeten worden onderzocht.

Discussie en toekomst perspectief

Uit de resultaten van dit proefschrift wordt duidelijk dat het nog steeds noodzakelijk is om de behandeling van functionele obstipatie te verbeteren, aangezien met de huidige behandel mogelijkheden één op de vier kinderen niet van hun klachten afkomen. Sommige kinderen hebben jarenlang obstipatie en dit kan zelfs voortduren tot op de volwassen leeftijd. Het ontwikkelen van nieuwe behandel strategieën is uitdagend. In de eerste plaats omdat het stellen van de diagnose van functionele obstipatie gebaseerd is op een cluster van symptomen, zonder dat er vandaag de dag gestandaardiseerde diagnostische onderzoeken beschikbaar zijn. Er is onvoldoende inzicht in de onderliggende oorzaken van obstipatie, waardoor de huidige behandeling voornamelijk symptomatisch is en onvoldoende gericht op oorzakelijke factoren. Een belangrijke eerste stap om zowel het inzicht in de onderliggende oorzaken als de behandeling van functionele darmproblemen te verbeteren, is het bereiken van een wereldwijde consensus over de definitie van deze aandoeningen. Recent heeft een groep experts op het gebied van de Kindergastroenterologie internationale consensus bereikt en de criteria voor functionele darmaandoeningen geformuleerd in de ROME III criteria 1,2. Als deze criteria ook daadwerkelijk wereldwijd geïmplementeerd worden, zou dat een enorme bijdrage kunnen leveren aan enerzijds het beter kunnen vergelijken van onderzoeksgegevens van verschillende onderzoekscentra, maar anderzijds ook de samenwerking tussen onderzoekscentra kunnen vergemakkelijken. Maar zelfs als deze criteria wereldwijd zouden worden gebruikt, kan men hier een kanttekening bij plaatsen. Aangezien de Rome III criteria voor functionele obstipatie bestaan uit een cluster van symptomen, moet men zich realiseren dat kinderen met obstipatie een heterogene patiëntengroep vormen. Men kan zich voorstellen dat kinderen met obstipatie zonder fecale incontinentie, een

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In dit proefschrift werden verschillende behandelmogelijkheden onderzocht die zijn gebaseerd op de huidige inzichten in de onderliggende oorzaken van obstipatie en factoren die obstipatie in stand zouden kunnen houden. In zuigelingen ontstaat obstipatie meestal rondom voedingsveranderingen, zoals op de overgang van borstvoeding naar flesvoeding of bij de introductie van bijvoeding. De samenstelling van flesvoeding verschilt in meerdere opzichten van die van borstvoeding en dit zou mogelijk een belangrijke oorzaak kunnen zijn voor verandering in het onlastingspatroon en het ontstaan van obstipatie. Er zijn continue ontwikkelingen gaande op het gebied van het vernieuwen van de samenstelling van flesvoeding voor baby’s, waarbij wordt geprobeerd deze samenstelling zoveel mogelijk te laten lijken op borstvoeding. De effecten en veiligheid van deze producten worden echter onvoldoende onderzocht in grote, goed opgezette studies. Desondanks worden de gezondheidseffecten van deze flesvoedingen, zoals een verbeterde stoelgang of afweer, vaak wel aangeprezen door de fabrikant. Dit geldt ook voor producten met toegevoegde pre- of probiotica die verkrijgbaar zijn voor oudere kinderen. Uitgebreider onderzoek naar zowel het effect en de veiligheid van deze producten is zeer belangrijk, voordat er dergelijke gezondheidseffecten aan gekoppeld kunnen worden. Een andere belangrijke oorzaak voor het ontstaan van obstipatie op de peuter- en kleuterleeftijd is het ophoudgedrag bij het voelen van aandrang. Tot onze teleurstelling was de speciaal ontwikkelde gedragstherapie voor kinderen met obstipatie gericht op dit ophoudgedrag en uitgevoerd door kinderpsychologen, niet succesvoller dan de standaardbehandeling bij de kinderarts. Er werd wel gezien dat gedragsproblemen in het algemeen veel voorkwamen bij kinderen met obstipatie. Het blijft echter de vraag of deze gedragsproblemen primair aanwezig zijn of ontstaan zijn ten gevolge van obstipatie en fecale incontinentie. Het lijkt dus belangrijk om kinderen met obstipatie te testen op gedragsproblemen, aangezien deze problemen van invloed zouden kunnen
zijn op het effect van de behandeling en de therapietrouw van deze patiënten. Verder onderzoek zou gedaan moeten worden of kinderen met specifieke gedragsproblemen beter te behandelen zijn met een speciaal ontwikkelde gedragstherapie dan de huidige standaardbehandeling.

Een andere subgroep binnen de groep kinderen met obstipatie lijken die kinderen te zijn die niet succesvol behandeld kunnen worden door zowel therapie met laxantia als via een gedragstmatige aanpak. Uit onderzoek in dit proefschrift bleek dat intensieve behandeling met laxantia, in de vorm van het wekelijks geven van rectale klysma’s, ook niet bijdroeg aan een betere klinische uitkomst. Men zou kunnen denken dat er bij deze kinderen met ernstige obstipatie sprake is van een gestoorde functie van de dikke darm. In de literatuur wordt beschreven dat kinderen met onbeheerlijke obstipatie mogelijk lijden aan een neuropathie (aandoening van de zenuwen) of myopathie (aandoening van de spieren) van het darmstelsel. Er werd in het verleden gedacht dat men door het meten van de exacte knijpbewegingen van het colon (=de dikke darm) middels een colon manometrie (=drukmeting) een onderscheid kon maken tussen zenuw of spier afwijkingen van de darm. In een recente studie is in kinderen met chronische obstipatie zowel gekeken naar de bevindingen bij colon manometrie als naar zenuwcellen en spierweefsel in stukjes van de dikke darm. Het bleek echter niet mogelijk om afwijkingen op weefsel niveau te koppelen aan de bevindingen van de drukmeting in de dikke darm. Verder onderzoek is dus nodig om te bepalen hoe afwijkingen bij drukmeting in de dikke darm overeenkomen met afwijkingen op weefsel niveau.

Naast dat de dikke darm een belangrijke rol heeft om met knijpbewegingen de darminhoud voort te bewegen, speelt de darm ook een rol in water- en zouthuishouding. Verandering in het opnemen van water uit de darm zou kunnen leiden tot een verandering in de samenstelling van de ontlasting en de motilititeit van de darm, hetgeen ernstige obstipatie kan veroorzaken. Het is bekend dat chloorkanalen in de darmwand een belangrijke rol spelen in het uitscheiden en opnemen van water en zout in de dikke darm. Stimulatie van chloor secretie veroorzaakt een passieve beweging van natrium en water naar de darmholte. Hierdoor ontstaat er een netto toename van isotone vloeistof in de darmholte met als gevolg een verbetering van de darmbewegingen. In recente onderzoeken bij volwassenen met obstipatie is aangetoond dat hun klachten afnamen door middel van een medicijn met als werking het activeren van chloor 2 kanalen. Op dit moment wordt ook binnen onze onderzoeksgroep gekeken of deze chloor kanalen een rol spelen in het ontstaan van obstipatie bij kinderen. Hopelijk zal dit onderzoek bijdragen aan ons inzicht in het ontstaan van obstipatie bij kinderen en mogelijk zelfs resulteren in verbetering van de behandeling.

Samenvatting & Discussie
Naast het ontwikkelen van nieuwe behandelmogelijkheden, is er in dit proefschrift onderzoek gedaan naar de prognose van obstipatie. Kennis over de prognose en factoren die deze prognose kunnen beïnvloeden is belangrijk voor het geven van accurate patiëntinformatie, voor een goede afweging van de juiste behandelstrategieën, en om eventueel kinderen met een hoog risico op langdurige klachten in een vroeg stadium te identificeren. Tot nu toe zijn er echter niet veel studies naar de prognose van obstipatie bij kinderen verricht. Deze studies zijn veelal uitgevoerd met inadequate onderzoeksmethodes. Daarnaast worden verschillende definities voor obstipatie gebruikt en wisselende uitkomstmatten. Op basis van in de literatuur gevonden gegevens over de prognose van obstipatie bij kinderen, konden geen goede conclusies getrokken worden.

In het algemeen wordt er aangenomen dat functionele obstipatie een milde aandoening is die uiteindelijk vanzelf weer over gaat. Uit de gegevens van ons lange termijn onderzoek zien we echter dat obstipatie bij kinderen lang niet altijd van voorbijgaande aard is. Het feit dat ongeveer een kwart van de kinderen ook nog obstipatie klachten heeft op volwassen leeftijd is zorgelijk. Tevens werd er gevonden dat kinderen met langdurige klachten een lagere gezondheidsgerelateerde kwaliteit van leven en een vertraagde levensloop hebben. Dit toont aan dat de gevolgen van obstipatie zich niet beperken tot de darm. Kinderen met chronische obstipatie lopen het risico dat ze minder ontwikkelingsmijlpalen bereiken en zowel op kinder- als op volwassenleeftijd een lagere kwaliteit van leven hebben. De artsen die deze kinderen behandelen moeten dus niet alleen aandacht hebben voor de symptomen van obstipatie, maar ook voor de gevolgen die obstipatie kan hebben op psychosociaal gebied. Verder onderzoek is nodig naar het vroegtijdig herkennen van de kinderen die het meest risico lopen op psychosociaal vlak en het ontwikkelen van preventieve maatregelen om dit risico te verkleinen.

Onderzoek op het gebied van functionele obstipatie bij kinderen blijft boeiend en uitdagend, aangezien er nog vele aspecten van deze aandoening verder onderzocht moeten worden. Het is van essentieel belang dat wereldwijd dezelfde definities voor functionele darmaandoeningen bij kinderen gehanteerd worden. Tot op heden is het inzicht in de vele factoren die een rol spelen bij het ontstaan en persisteren van deze klachten nog steeds beperkt. Er zullen bruikbare en betrouwbare diagnostische onderzoeken ontwikkeld moeten worden. Meer doelgerichte behandelstrategieën, zowel gericht op de symptomen van obstipatie als op het aanpakken van de secundaire gevolgen op psychosociaal gebied, zijn noodzakelijk. Deze ontwikkelingen zouden
uiteindelijk moeten leiden naar een verbetering van de prognose en de kwaliteit van leven van kinderen met obstipatie.

REFERENCES


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Dankwoord

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