Childhood constipation treatment, long-term prognosis and quality of life
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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. 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

