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

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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>
<thead>
<tr>
<th>Table 1. Baseline characteristics (n=401)</th>
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<td>Age, years</td>
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<td>25th – 75th percentiles</td>
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<td>Gender, %</td>
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<td>Male</td>
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<td>Age of onset, years</td>
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<td>Defecation frequency / week</td>
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<td>25th – 75th percentiles</td>
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<td>Fecal incontinence frequency / week</td>
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<td>25th – 75th percentiles</td>
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<td>≥2 / week, %</td>
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<td>Large stools, %</td>
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<td>Abdominal pain, %</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).

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 patient 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, 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.

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. 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. To date, comparison to other follow-up studies is still hampered by differences in applied definitions of constipation, small numbers of patients, low follow-up percentages, or due to retrospective or cross-sectional study designs instead of longitudinal ones.

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. 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. 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. 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. 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
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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. 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. 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. 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

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