Gastrointestinal motility disorders in children: etiology and associated behaviors

Peeters, B.

Citation for published version (APA):
Completion of toilet training in children with defecation disorders and concomitant symptoms of autism spectrum disorders

Babette Peeters, Ilse L. Noens, Sofie Kuppens, Marc A. Benninga
Abstract

Objective
The presence of a functional defecation disorder (FDD) may delay the moment of completion of toilet training. However, the association between the presence of symptoms of autism spectrum disorders (ASD) and the moment of completion of toilet training in patients with FDD is unknown. In this study we assess the moment of completion of toilet training in children with FDD with and without concomitant symptoms of ASD and controls.

Methods
Consecutive children (4-12 yrs) presenting with FDD according to the ROME III criteria were screened for symptoms of ASD by two validated questionnaires; the Social Responsiveness Scale (SRS) and the Social Communication Questionnaire-Lifetime (SCQ-L). Children were defined as having symptoms of ASD when they scored at or above the cut-off value on one or two questionnaires (SRS≥51; SCQ≥15). Controls (4-12 yrs) were recruited from primary schools. Toilet training characteristics were compared.

Results
In total, 242 children with FDD were included, of which 70 showed symptoms of ASD. The control group consisted of 96 children. Significantly less children with FDD and ASD symptoms were toilet trained for stools and urine during daytime before the age of 4 yrs (45% and 62%) than children with FDD only (60% and 76%), whereas almost all controls had completed toilet training for stools and urine during daytime before this age (95% and 98%).

Conclusion
Children with FDD and ASD symptoms completed toilet training both for stools and urine during daytime at a significantly later age than children with FDD only and controls.
Introduction

Functional defecation disorders (FDD), such as functional constipation and functional non-retentive fecal incontinence, are common problems in childhood that may negatively affect quality of life.(1-3) The pathophysiology of FDD is classically considered to be complex and multifactorial. Environmental, genetic, behavioral factors, and child-parent interactions have all been subject of research and seem to play a role in the etiology or persistence of symptoms.(2;4) However, the exact pathophysiology of FDD is incompletely understood. In a large proportion of children, symptoms of FDD arise in the period of toilet training.(5) Indeed, the presence of an FDD has been associated with a delayed completion of toilet training for stools and urine.(6-8) Furthermore, atypical toileting behavior, for instance stool toileting refusal and hiding away while defecating, has been associated with late completion of toilet training and the presence of constipation.(9;10) For many parents of children with FDD, difficulties in getting their child toilet trained is a major concern, as being toilet trained is one of the prerequisites for admission to most primary schools.

In the literature, FDD have frequently been associated with autism spectrum disorders (ASD).(11-16) In the general population, a prevalence rate of ASD of 0.6% - 0.7% has been reported.(17) The term ‘ASD’ represents three pervasive developmental disorders as defined in the Diagnostic and Statistical Manual of Mental disorders (DSM-IV-TR): autistic disorder, Asperger syndrome and pervasive developmental disorder – not otherwise specified (PDD-NOS).(18) ASD are characterized by impairments in social interaction, in verbal and non-verbal communication, and the presence of restricted, repetitive and stereotyped patterns of behavior, interests and activities.(19) In children with ASD, toilet training problems are commonly present. For these children, toilet training has been reported to be completed at a later moment compared to controls and after being toilet trained, regression in training skills often occurs due to a change in routines.(20;21)

The association between the presence of concomitant symptoms of ASD and the moment of completion of toilet training in children with FDD is, however, unknown. It could be hypothesized that the presence of concomitant ASD symptoms further delays the moment of completion of toilet training in children with FDD. Identifying children with FDD and concomitant symptoms of ASD is important as these children might benefit from an early adaptation of the regular treatment strategies, for instance by adding psycho-educational, psycho-therapeutic or psychiatric care to the standard therapy for FDD.

As such, the aim of this study was to compare the moment of completion of toilet training between children with FDD without ASD symptoms, children with FDD with concomitant symptoms of ASD and controls.
Materials and Methods

Participants

Between September 2009 and October 2011, consecutive patients, aged 4-12 years, referred to the outpatient clinic of a tertiary hospital in Amsterdam, The Netherlands, with a diagnosis of functional constipation (FC) or functional non-retentive fecal incontinence (FNRI) according to the internationally accepted ROME III criteria, were included after informed consent was obtained from the parents. Patients were excluded from participation if they suffered from a known pathology causing constipation and/or fecal incontinence, such as chronic inflammatory bowel disease (Crohn’s disease or ulcerative colitis), celiac disease, or when they had a history of large bowel surgery, congenital anorectal malformations, neurological disease (complete spinal cord transection, multiple sclerosis or spina bifida) or a genetic syndrome. Furthermore, patients with a known intellectual disability and/or an intelligence quotient below 70 were excluded.

Parents or caregivers filled out two validated ASD screening questionnaires about their child (Social Responsiveness Scale (SRS) and Social Communication Questionnaire – Lifetime (SCQ-L). Children were considered to have symptoms of an ASD when they scored on or above the validated cut-off values of one or both questionnaires. For the SRS a cut-off value of ≥ 51 was used and for the SCQ-L a cut-off value of ≥ 15 was applied. Children with FDD were divided in to two groups; one group with FDD without symptoms of ASD and another group with FDD with concomitant symptoms of ASD. This division was based on the results of the two ASD screening questionnaires.

Controls, aged 4 to 12 years, were recruited from primary schools in the province of Limburg, Flanders, Belgium. Children with an FDD according to the ROME III criteria and/or an ASD diagnosis were excluded from participation. Children with a history of a diagnosis of FDD made by a medical doctor or prior or current treatment with laxatives were also excluded.

The local Medical Ethics Committee waived the need for informed consent.

Children with FDD with and without symptoms of ASD

During the first visit at the outpatient clinic, as part of our routine procedure, a standardized defecation questionnaire was filled out by the medical doctor. This defecation questionnaire consists of questions about the medical history of the child, social environment, medication use, moment of completion of toilet training (stools, urine during daytime and urine during nighttime) and specific questions about bowel habits and defecation pattern based on the internationally accepted ROME III criteria for functional defecation disorders.
Controls
Parents of controls were informed about the study by written and verbal information. Parents of participating children were asked to fill out a bowel habit diary together with their child for a period of one week. After this week, a structured interview that included the standardized defecation questionnaire as described above was performed by telephone by a trained investigator. The presence of an FDD or ASD was ruled out by the structured interview with the parents and the interpretation of the bowel habit diary.

Outcomes
The primary outcomes of this study were the moment of completion of toilet training for stools, urine during daytime, and urine during nighttime in children with FDD without symptoms of ASD, children with FDD with concomitant symptoms of ASD and controls. A child was considered toilet trained for stools, or urine during daytime when the child defecated or urinated in the toilet or potty in the majority of time for at least one month. Children, however, who had been completely toilet trained for stools but currently suffered from fecal incontinence due to FC or FNFRI were considered to be toilet trained. A child was considered to be toilet trained at night when the child had experienced nighttime bladder control for the majority of time for at least one month. The percentage of children who had completed toilet training before the age of 4 years and at the time of the study was compared between the three study groups. Furthermore, the age of completion of toilet training in children who had completed toilet training at the time of the study was compared between the three groups.

Statistical Analysis
The statistical program SPSS version 16.0 (SPSS Inc, Chicago Ill) was used for statistical analyses. Skewed continuous data were compared between the three study groups by Kruskall-Wallis tests. To compare the proportions of children that completed toilet training between the three study groups, Fisher exact tests were performed. Effect sizes for the comparisons between the three study groups were reported as eta square ($\eta^2$) in case of continuous variables and as Cramer’s V in case of dichotomous variables. Follow-up comparisons between the subgroups included Mann-Whitney U tests and Chi-square analyses. The significance level was set at <.05. P-values resulting from follow-up comparisons between the subgroups were corrected for multiple testing by Holms’ sequential Bonferroni correction.
Results

Demographics

During September 2009 and October 2011, 242 children with FDD participated in this prospective study. The majority of children with FDD suffered from FC (91%). Seventy children (29%) had symptoms of ASD according to the scores on the ASD screening questionnaires. In thirteen patients (5.4%), a diagnosis of an ASD had previously been made. Of these, one child was diagnosed with classical autism, two with Asperger Syndrome and ten with PDD-NOS. The remaining 172 patients fulfilled the criteria of FDD without having ASD symptoms.

In the province of Limburg in Flanders, Belgium, parents of 909 children from primary schools were asked to participate in this study. Disappointingly, parents of only 124 children gave informed consent to participate in this study. Of these, 21 fulfilled the criteria of FC (17%) and these children were excluded. There were no children fulfilling the criteria of FNRFI. For seven of the remaining 103 children, too many data were missing to exclude a diagnosis of FDD with certainty. Those seven children were also excluded from the analyses. There were no children with a known or presumed diagnosis of an ASD as reported by the parents. This resulted in a total number of ninety-six controls that were included in the analyses. The baseline characteristics of the FDD patients without ASD symptoms, the FDD patients with concomitant ASD symptoms and general population controls are depicted in Table 1. Children with FDD and concomitant symptoms of ASD were significantly older at the time of study than children with an FDD only and general population controls;

Table 1 | Baseline characteristics of the three study groups

<table>
<thead>
<tr>
<th></th>
<th>FDD only 1</th>
<th>FDD with ASD symptoms 1</th>
<th>Controls 1</th>
<th>Comparison of 3 study groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>172</td>
<td>70</td>
<td>96</td>
<td>-</td>
</tr>
<tr>
<td>Male</td>
<td>88 (51%)</td>
<td>43 (61%)</td>
<td>42 (44%)</td>
<td>ns</td>
</tr>
<tr>
<td>Median age in years</td>
<td>7.7 (IQR 5.5; 9.4)†</td>
<td>8.4 (IQR 6.6; 10.3) †*</td>
<td>7.2 (IQR 5.6; 9.5)*</td>
<td>H (2, N = 338) = 5.73; p = .06; η² = .02</td>
</tr>
<tr>
<td>Diagnosis FC without FI</td>
<td>43 (25%)</td>
<td>10 (14%)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Diagnosis FC with FI</td>
<td>116 (67%)</td>
<td>51 (73%)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Diagnosis FNRFI</td>
<td>13 (8%)</td>
<td>9 (13%)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Median age start symptoms in years</td>
<td>3.0 (IQR 0.5; 4.0)</td>
<td>3.0 (IQR 0; 4.0)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Duration of symptoms in years</td>
<td>4.5 (IQR 2.6; 6.5) *</td>
<td>5.5 (IQR 3.6; 7.7) *</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

FDD = Functional Defecation Disorder ; ASD = Autism Spectrum Disorder ; IQR = Inter Quartile Range; FC = Functional Constipation ; FI = Fecal Incontinence; FNRFI = Functional Non-Retentive Fecal Incontinence ; ns = non significant ; n/a = not applicable. 1Same superscripts represent the presence of a significant difference between the subgroups based on follow-up comparisons using Holms’ sequential Bonferroni correction for multiple testing when applicable (adjusted p-values: .017; .025; .05).
the median duration of FDD symptoms was significantly longer in the study group with ASD symptoms compared to the group with FDD without ASD symptoms. There were no significant differences in gender distributions between the three groups. There were also no significant differences in type of FDD diagnosis between the two groups with FDD.

Toilet trained for stools

As shown in Table 2, the percentage of children that had completed toilet training for stools at the time of study was significantly higher in the control group compared to the two study groups with an FDD diagnosis. The median age at which toilet training for stools had been completed, was significantly lower in the FDD group with concomitant symptoms of ASD than in children with FDD only and controls. The percentage of children

| Table 2 | Toilet training characteristics of the study groups for stools and urine |
|-----------------------------------------------|--------------------------|--------------------------|--------------------------|
| STOOLS                                       | FDD only¹ (n = 172)       | FDD +ASD symptoms¹ (n = 70) | Controls¹ (n = 96)       | Comparison of 3 study groups |
| Toilet training completed before age of 4 years | 97 (56%)*                | 29 (41%)*                | 91 (95%)*                | X² (2, N = 323) = 52.13; p < .001; Cramer’s V = .40 |
| Toilet training completed at time of study    | 133 (78%)*               | 49 (70%)*†               | 95 (99%)*†               | X² (2, N = 336) = 26.26; p < .001; Cramer’s V = .28 |
| Age at completion of toilet training (median)  | 3.0 (IQR 2.5; 3.5)*      | 3.5 (IQR 3.0; 4.0)*      | 3.0 (IQR 2.0; 3.0)*      | H (2, N = 257) = 37.4; p < .001; η² = .15 |

| URINE DAYTIME                                |                          |                          |                          |
| Toilet training completed before age of 4 years | 124 (72%)*               | 41 (58%)*                | 94 (98%)*                | X² (2, N = 326) = 33.7; p < .001; Cramer’s V = .32 |
| Toilet training completed at time of study    | 155 (90%)*               | 60 (86%)*†               | 95 (99%)*†               | X² (2, N = 338) = 10.53; p < .005; Cramer’s V = .18 |
| Age at completion of toilet training (median)  | 3.0 (IQR 2.5; 3.5)*      | 3.0 (IQR 3.0; 4.0)*      | 2.0 (IQR 2.0; 3.0)*†      | H (2, N = 294) = 40.3; p < .001; η² = .14 |

| URINE NIGHTTIME                              |                          |                          |                          |
| Toilet training completed before age of 4 years | 86 (50%)*               | 28 (40%)*†               | 71 (74%)*†               | X² (2, N = 327) = 18.9; p < .001; Cramer’s V = .24 |
| Toilet training completed at time of study    | 127 (74%)*               | 50 (70%)*†               | 89 (93%)*†               | X² (2, N = 338) = 15.0; p < .001; Cramer’s V = .22 |
| Age at completion of toilet training (median)  | 3.4 (IQR 2.5; 4.0)       | 3.5 (IQR 3.0; 4.5)*      | 3.0 (IQR 2.0; 3.0)*      | H (2, N = 248) = 11.3; p = .004; η² = .05 |

FDD = Functional Defecation Disorder ; ASD = Autism Spectrum Disorder ; IQR = Inter Quartile Range. ¹Same superscripts represent the presence of a significant difference between the subgroups based on follow-up comparisons using Holms’ sequential Bonferroni correction for multiple testing (adjusted p-values: .017; .025; .05)
who had completed toilet training for stools before the age of 4 years was the lowest in the FDD group with concomitant symptoms of ASD.

Toilet trained for urine during daytime
Nearly all controls had completed toilet training for urine during the daytime at the moment of study (Table 2), which was in contrast with children with FDD with or without ASD symptoms. The median age at which toilet training for urine during daytime was achieved was not statistically different between the two FDD groups. However, a significantly higher proportion of children with FDD only had completed toilet training for urine during daytime before the age of 4 compared to children with FDD with concomitant ASD symptoms.

Toilet trained for urine during nighttime
Significantly more children in the control group had completed toilet training for urine during the nighttime at the moment of study compared to the group with FDD only and the group with FDD and ASD symptoms (Table 2). No significant differences in moment of completion of toilet training for urine during nighttime existed between the FDD groups with and without symptoms of ASD (Table 2).

Discussion
This is the first study comparing the moment of completion of toilet training for stools and urine between children with FDD with concomitant ASD symptoms, children with FDD only and controls. As hypothesized, a significantly lower percentage of children with FDD and concomitant ASD symptoms completed toilet training for stools and urine during daytime before the age of 4 years compared to children with FDD without ASD symptoms and controls.

Becoming toilet trained is an important milestone in a child’s life and a step forward in achieving more independence. The moment of initiation and completion of toilet training depends on an individual child’s level of physical and psychological maturation, e.g. their ability to sit, walk, express their needs and to understand and respond to both their own sensations and parental instructions. In the general population, the mean age at which completion of daytime toilet training for stools and urine is achieved has been reported to be 32 to 39 months. Largo et al. studied completion of toilet training in a sample of almost 500 children and found that at the age of four, about 90% of both girls and boys was found to be completely toilet trained during daytime for stools and urine. In 2004, Blum et al. reported 84% of children to be completely daytime toilet trained at the age of 3.5 years and described children not being toilet trained at this age as ‘late toilet trainers’. These late toilet trainers were more likely to show stool toileting refusal, to
hide when defecating, to be frequently constipated and to have lower language scores at 18 months of age.

In contrast with the general population and the controls in this study, we found that only 56% and 72% of the children with an FDD were toilet trained for stools and urine during daytime before the age of 4 years. An association between late completion of toilet training and the presence of FDD has been described before, although a clear explanation for this phenomenon is lacking.(6-8) Toilet refusal, which is the result of fear for the toilet in some children or can be one of the characteristics of a stubbornness in toddlers, often precedes FDD.(31) This may lead to withholding behavior with painful evacuation of hard and large stools and eventually in disturbed sensation of urge due to fecal impaction. Another hypothesis is that shame or parental punishment and pressure might be involved in problematic toilet training of children with FDD.(32) Moreover, behavioral problems might hamper typical toilet training in children with FDD.(33;34)

In the group of children with FDD and concomitant symptoms of ASD, we found even lower percentages of children that had completed toilet training before the age of 4 years. In these patients, who were significantly older than the children with FDD only and controls with a median age of 8.4 years, the percentage that had completed toilet training at the time of study was only 70% for stools and 86% for urine during daytime. Children with ASD often experience difficulties in coping with changes in routines and may have specific and limited interests and behaviors. This can make it a challenge to learn children with ASD or ASD symptoms to use the potty or toilet as a new routine. A study by Dalrymple et al., describing parental views on toilet training children with ASD, showed that next to toilet training refusal, there are many problems that ASD children present with during the toilet training period.(21) Among the most commonly found were stuffing up toilets, continually flushing, playing in the toilet, refusal to use other toilets or smearing feces. These behavioral factors, but also sensory, motor and cognitive factors may hinder the toilet training process. In the study by Dalrymple et al., lower cognition and lower verbal levels were significantly related to a higher age at completion of toilet training.(21) In our study, however, children with a known intellectual disability were excluded from participation. This might indicate that delayed completion of toilet training found in children with FDD and concomitant ASD symptoms in this study is not likely to be the result of their general level of cognitive functioning. Still, problems in making sense and executive dysfunction may play an important role in toilet training problems seen in children with ASD symptoms. It is known that in people with ASD, executive dysfunction, in particular a deficit in cognitive flexibility, is strongly associated with resistance to changes and the presence of restricted interests and activities.(35)

One may also hypothesize that parents of children with ASD or ASD symptoms are more likely to postpone the initiation of toilet training due to the presence of other behavioral problems the parents have to cope with. Unfortunately, in this study no data were available to assess the moment of initiation of toilet training in the study groups.
Recently, the existence of a Broader Autism Phenotype was shown in fathers of children with ASD (36). ASD symptoms were more commonly found in these fathers compared to fathers of children without ASD. The presence of ASD symptoms in one of the parents might also play a role in the success of guiding their child with ASD or ASD symptoms and FDD towards a typical toilet training status.

This study has some limitations. As the site of recruitment for patients with FDD was a specialized referral center for motility disorders, there might have been a bias in the selection of patients. However, more than a third of patients have been referred directly by their GP and have never been treated before by a pediatrician or pediatric gastroenterologist for their FDD. A second limitation is that patients with FDD were screened for ASD symptoms using two validated screening instruments but were not subjected to an extensive standardized assessment including direct observation and a detailed developmental history taking, which are mandatory to make a definite diagnosis of an ASD. However, the cut-off values for the screening instruments used in this study have been validated in the general population and have shown a good correlation with standardized observation and developmental history instruments. The control group was not screened for ASD symptoms in a similar way, but it may be expected that the results from recent validation studies are a good representative for the general population. The response rate of the general control group was very low. Nevertheless, the toilet training results of this group are very similar to the results of the general population as previously published in literature. The diagnosis of FDD in the control group was based on the ROME III criteria. One of the five criteria for functional constipation in childhood is the presence of a large fecal mass in the rectum. Due to ethical objections, the presence of this criterion could not be assessed in the control group. Therefore, we might have missed some children with FDD in the control group. Lastly, it was found that a substantial amount of parents of children that had completed toilet training at the time of the study, did not remember the exact moment of completion of toilet training of their child. Therefore, the assessment of the median age at which toilet training was achieved in the subgroups is based on a small group of children. As a result, less profound differences are observed in the comparison analyses of the median ages between the groups. However, we found large differences in the comparison of the proportions of children being toilet trained before the age of 4, which is a clinically relevant and more reliable item of information as all included children were 4 years or older.

Nevertheless, this study underlines that clinicians should be alert for ASD symptoms in children presenting with FDD and toilet training problems. The effect of adding specialized care to the regular treatment protocols for FDD in children with concomitant ASD symptoms should be assessed by means of randomized controlled trials. Future studies should shed more light on the sensory, motor, behavioral, and cognitive aspects of delayed toilet training in FDD children with concomitant ASD symptoms.
Conclusion

Children with FDD and ASD symptoms completed toilet training for stools at a significantly later age than children with FDD only and controls. The percentage of children being toilet trained for stools or urine during daytime before the age of four was significantly lower in the FDD group with concomitant symptoms of an ASD compared to children with an FDD only or controls. Further investigations are needed to unravel the motor, sensory, behavioral, and cognitive factors that may be involved.
Reference List


