Gastrointestinal motility disorders in children: etiology and associated behaviors

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Symptoms of Autism Spectrum Disorders in Children with Functional Defecation Disorders

Babette Peeters, Ilse Noens, Elise M. Philips, Sofie Kuppens, Marc A. Benninga
Abstract

Objective
In children with autism spectrum disorders (ASD), a remarkably high prevalence of functional defecation disorders (FDD) has been found. This study prospectively assesses the prevalence of ASD symptoms in children presenting with FDD.

Study design
Children (4 -12 yrs) with functional constipation (FC) or functional non-retentive fecal incontinence (FNRFI) according to the ROME III criteria referred to a specialized outpatient clinic were included. Parents completed two validated ASD screening questionnaires about their child; the Social Responsiveness Scale (SRS) and the Social Communication Questionnaire Lifetime (SCQ-L). A total SRS score of $\geq 51$ is a strong indicator for the presence of ASD. On the SCQ-L, a score of $\geq 15$ is suggestive for ASD.

Results
In total, 242 patients (130 males, median age 7.9) were included. Of these, 91% were diagnosed with FC and 9% with FNRFI. Thirteen children (5.4%) had previously been diagnosed with ASD. Twenty-six children (11%) had both SRS and SCQ-L scores at or above cutoff points, strongly suggestive for the presence of ASD. Solely high SRS were present in 42 children (17%), whereas two children (1%) only had high SCQ-L scores. Altogether, 29% had ASD symptoms, indicated by SRS and/or SCQ-L scores at or above the cut off values. These children were older than children without ASD symptoms and presented with a longer duration of symptoms.

Conclusions
A substantial amount of children (29%) presenting with FDD at a tertiary hospital has concomitant ASD symptoms. Clinicians should be aware of ASD symptoms in children with FDD.
Introduction

Functional defecation disorders (FDD), functional constipation (FC) and functional non-retentive fecal incontinence (FNRFI), are common problems in children. The world-wide prevalence of functional constipation (FC) in children ranges from 0.7 to 29.6%. Fecal impaction may lead to fecal incontinence which can be a source of considerable distress and embarrassment for the child and the family. In some children, fecal incontinence may occur without signs of fecal retention better known as ‘functional non-retentive fecal incontinence’ (FNRFI). FNRFI has a reported prevalence of 1.5 to 9.8% in children. The internationally accepted ROME III diagnostic criteria for FC and FNRFI are tabulated in Table I.

Despite maximal appliance of current conservative treatment modalities, long term follow-up data show that FDD symptoms persist into adulthood in 25-30% of children, negatively affecting quality of life.

The pathophysiology of FDD is multifactorial and largely unknown. Genetic factors are thought to play a role, but also environmental factors, behavior problems and child-parent interactions may contribute to the etiology and persistence of symptoms. Interestingly, a high prevalence of gastrointestinal disorders, most frequently being constipation, has been reported in children with autism spectrum disorders (ASD). ASD represent three of the pervasive developmental disorders 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). Individuals affected by ASD may share a common triad of impairment in social interactions, impaired and atypical verbal and non-verbal communication, and repetitive and unusual behavior and play.

The prevalence of ASD in children in the general population is estimated to range from

| Table I | Diagnostic ROME III criteria for functional constipation and functional non-retentive fecal incontinence |
|--------------------------------------------------|
| Functional constipation (FC)
  Must include 2 or more of the following in a child with a developmental age of at least 4 years with insufficient criteria for diagnosis of IBS: |
| Functional non-retentive fecal incontinence (FNRFI)
  Must include all of the following in a child with a developmental age at least 4 years: |
| 1. Two or fewer defecations per week |
| 2. At least 1 episode of fecal incontinence per week |
| 3. History of retentive posturing or excessive volitional stool retention |
| 4. History of painful or hard bowel movements |
| 5. Presence of a large fecal mass in the rectum |
| 6. History of large diameter stools that may obstruct the toilet |
| 1. Defecation into places inappropriate to the social context at least once 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 of autism spectrum disorders
Recent data from the United States however provide evidence for a current prevalence over 1% (11.3 per 1,000). Reliable data on the prevalence of ASD symptoms in children presenting with FDD, diagnosed according to internationally accepted criteria, are sparse. Recently, a retrospective study was published investigating the prevalence of a history of diagnosed ASD in children with FC according to the former ROME II criteria. Nearly 8.5% of the children were reported to have an ASD history. An Australian study investigated self-reported ASD traits in young adults who had been referred for gastrointestinal symptoms in early life. Constipation was not defined by validated criteria and a broad spectrum of symptoms was considered to be the result of constipation. No relation between gastrointestinal symptoms in early life and ASD traits in young adulthood could be demonstrated.

A validated assessment of the prevalence of ASD symptoms in children presenting with FDD is needed to further clarify the possible association between the two disorders and to obtain better insight in the complex pathophysiology of both FDD and ASD. Moreover, confirming a high prevalence of ASD symptoms in children with FDD may give rise to an adaptation of the current standard diagnostic work-up and therapeutic strategies for FDD in children.

In this study, we prospectively and systematically assessed the prevalence of ASD symptoms in children presenting with FDD.

**Study design**

**Study population**

A prospective cohort study was carried out between September 2009 and October 2011 in a specialized tertiary referral center for children with FDD at the Emma Children’s Hospital, Academic Medical Centre in Amsterdam, The Netherlands. A total of 302 consecutive children, aged 4-12 years, presenting at the outpatient clinic with a diagnosis of FC or FNRFI according to the internationally accepted ROME III criteria were asked to participate in this study. Patients were excluded from participation if they suffered from known pathology causing constipation and/or fecal incontinence, such as chronic inflammatory bowel disease, 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 of less than 70 were excluded. After giving informed consent, parents filled out two specific ASD screening questionnaires about their child. With a known prevalence of ASD in the normal population of 0.6%, a sample size of 223 children would be required to achieve a power of 80% with an alpha
of 5% to detect a difference in prevalence that is at least 5 times higher than in the normal population. This study was approved by the Medical Ethics Committee of the Academic Medical Center in Amsterdam.

**Instruments**

*Standardized defecation questionnaire*

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, presence of a prior ASD diagnosis, medication use and specific questions about the defecation pattern based on the ROME III criteria. A prior ASD diagnosis was defined as a diagnosis according to the DSM-IV-TR criteria made by a multidisciplinary team.

*Social Responsiveness Scale*

The Social Responsiveness Scale (SRS) is a validated 65-item quantitative ASD screening questionnaire developed in 2005 to assess a wide range of interpersonal behavior, communication and repetitive/stereotypic behavior characteristics of ASD. Items are scored on a 4-point scale, ranging from ‘not true’ to ‘always true’. The raw total score ranges from 0 to 195, with higher scores indicating more ASD symptoms. In 2011, the cut off value for raw scores in the Dutch population with normal intelligence was set at 51, with a score of ≥51 being suggestive for a diagnosis of ASD with a sensitivity of .90 and a specificity of .88 for both males and females. The manual also provides T-scores for clinical use, with T=60 being the proposed cut off for clinically significant ASD traits. The SRS has proven to be a reliable and valid instrument, with good psychometric properties and discriminant validity and good agreement with the Autism Diagnostic Interview – Revised.

*Social Communication Questionnaire-Lifetime*

The Social Communication Questionnaire (SCQ) is a validated quantitative screening questionnaire for ASD in children of 4 years and older developed in 2003. The SCQ consists of 40 yes or no items to be completed by the parent resulting in a total score between 0 and 40. The agreement between SCQ scores and scores on the more extensive Autism Diagnostic Interview is high. The SCQ-Lifetime (SCQ-L) version of the SCQ aims at traits of ASD in the entire developmental history of children. A total score of ≥15 on the SCQ-L is suggestive for the presence of ASD with a sensitivity of .90 and a specificity of .80. The reliability and validity of the Dutch version of the SCQ-L have been approved.
Outcome

The primary outcome is the prevalence of ASD symptoms in children with FDD. The presence of ASD symptoms was defined as a score at or above the cut off value on one or two ASD screening questionnaires (total raw SRS score of $\geq 51$ and/or total SCQ-L score of $\geq 15$). Scoring at or above the cut off value on one of the two questionnaires was considered to be suggestive for the presence of an ASD. Scoring at or above the cut off values of both questionnaires was considered to be very suggestive for the presence of an ASD. The secondary outcome is the difference in clinical characteristics between patients with and without ASD symptoms.

Statistical Analysis

For all statistical analyses SPSS version 16.0 (SPSS Inc, Chicago Ill) was used. Missing SRS values were imputed by the median value of the standardization sample; missing SCQ values by the normative (derived) score (0). A maximum of 10 percent missing values was considered acceptable. Total raw scores on the SRS and total raw scores on the SCQ-L were analyzed as continuous variables. For the comparison of proportions, Chi square analyses were performed. Fisher exact tests were performed to compare proportions with an observed or expected frequency of less than 5. Continuous data were compared by independent t-tests when normally distributed. For the comparison of skewed continuous data, Mann-Whitney U tests were performed. The significance level was set at $<.05$.

Results

Demographics

Out of 302 patients, parents of three patients refused to participate. The response rate was 83%; parents of a total of 250 patients returned both ASD screening questionnaires. Three patients were excluded because of a known IQ $<70$ and one because of a chromosomal abnormality (22q11 deletion) known to be associated with both constipation and ASD.\textsuperscript{5}\textsuperscript{,23} Because four patients had to be excluded due to too many missing values, data of 242 patients were used in the analyses. Thirty-five percent of the patients were referred to the outpatient clinic by a general practitioner (GP) and had never been treated by a pediatrician or pediatric gastroenterologist for their FDD.

Baseline characteristics of the 242 patients included in the analyses are depicted in Table II. Of all 242 participating children, 133 (55%) were male. Median age of participants was 7.9 years (IQR 5.7-9.5).

Only 9% of the patients were diagnosed with FNRFI, all other patients fulfilled the criteria of FC. The majority of FC patients (76%) suffered from fecal incontinence.
FDD symptoms had started at a median age of 3.0 years (IQR 0.5-4.0) and the median duration of symptoms was 4.7 years (IQR 2.9-6.9). In thirteen patients (5.4%), a diagnosis of ASD had previously been made. Of these, one child was diagnosed with classical autism, two with Asperger Syndrome and ten with PDD-NOS. Ten out of these thirteen patients suffered from FC and the remaining three patients fulfilled the criteria of FNRFI. In another four participants, the presence of ASD had been suspected previously but no definite diagnosis had yet been made.

In five children, the use of psychopharmaca registered for treatment of ADHD symptoms was reported.

**ASD symptoms**

SRS and SCQ-L scores were calculated for all 242 children and are summarized in Table III. Sixty-eight patients (28%) scored at or above the SRS cut off value, whereas 28 patients (12%) scored at or above the SCQ-L cut off value. Of all participants, 26 (11%) scored above the critical values of both questionnaires. Critical scores on the SRS only were found in 42 patients (17%), two patients (1%) only exceeded the SCQ-L cut off value. The percentage of children with ASD symptoms on one or two of the screening questionnaires in the group of constipated children did not differ significantly from the percentage found in FNRFI patients (28% vs. 41% resp., \(X^2=1.69, p=.19\)).

Altogether, 29% (n = 70) of the participating children with FDD had ASD symptoms as indicated by SRS and/or SCQ-L scores above the cut off value. All 13 children (5.4%) with a prior diagnosis of ASD had critical scores on one (n = 3) or two ASD (n = 10) screening questionnaires in this study. Of the four participants for whom the presence of ASD had

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**Table II | Demographics**

<table>
<thead>
<tr>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Median age in years</td>
</tr>
<tr>
<td>Diagnosis functional constipation without fecal incontinence</td>
</tr>
<tr>
<td>Diagnosis functional constipation with fecal incontinence</td>
</tr>
<tr>
<td>Diagnosis functional non-retentive fecal incontinence</td>
</tr>
<tr>
<td>Median age start symptoms in years</td>
</tr>
<tr>
<td>Duration of symptoms in years</td>
</tr>
<tr>
<td>Treated by general practitioner only</td>
</tr>
<tr>
<td>Known with autism spectrum disorder</td>
</tr>
<tr>
<td>Autism spectrum disorder previously suspected</td>
</tr>
<tr>
<td>Use of psychopharmaca</td>
</tr>
</tbody>
</table>

IQR = Inter Quartile Range
been suspected previously, three scored above the cut off values of both questionnaires and one only had critical SRS scores.

Clinical characteristics of patients with and without ASD symptoms

Clinical characteristics of children with ASD symptoms were compared with those of children without ASD symptoms according to the two screening questionnaires (see Table IV). The 70 children with ASD symptoms were significantly older at time of presentation than their peers with normal scores on both questionnaires (8.4 vs. 7.7 years, $U=4962; z=-2.14; p=0.032$). Sex distribution and type of functional defecation disorder did not differ significantly between the groups. Children with ASD symptoms had a significantly longer

Table III | Presence of symptoms of autism spectrum disorders

<table>
<thead>
<tr>
<th>Patients (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median SRS score</strong></td>
</tr>
<tr>
<td><strong>Median SRS t-score</strong></td>
</tr>
<tr>
<td><strong>Cases with SRS score ≥ cut off value</strong></td>
</tr>
<tr>
<td><strong>Median SCQ-L score</strong></td>
</tr>
<tr>
<td><strong>Cases with SCQ-L score ≥ cut off value</strong></td>
</tr>
<tr>
<td><strong>Cases with SRS or SCQ-L ≥ cut off value</strong></td>
</tr>
<tr>
<td><strong>Cases with both SRS and SCQ-L ≥ cut off value</strong></td>
</tr>
<tr>
<td><strong>ASD symptoms</strong></td>
</tr>
</tbody>
</table>

*SRS = Social Responsiveness Scale; SCQ-L = Social Communication Questionnaire-Lifetime; IQR = Inter Quartile Range; ASD = Autism Spectrum Disorder*

Table IV | Clinical characteristics of patients with and without symptoms of autism spectrum disorders according to SRS and/or SCQ-L

<table>
<thead>
<tr>
<th></th>
<th>No ASD symptoms</th>
<th>ASD symptoms</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>172 (71%)</td>
<td>70 (29%)</td>
<td>-</td>
</tr>
<tr>
<td>Male</td>
<td>90 (52%)</td>
<td>43 (61%)</td>
<td>0.197</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>0.032*</td>
</tr>
<tr>
<td>Diagnosis FC without FI</td>
<td>43 (25%)</td>
<td>10 (14%)</td>
<td>0.068</td>
</tr>
<tr>
<td>Diagnosis FC with FI</td>
<td>116 (67%)</td>
<td>51 (73%)</td>
<td>0.409</td>
</tr>
<tr>
<td>Diagnosis FNRFI</td>
<td>13 (8%)</td>
<td>9 (13%)</td>
<td>0.194</td>
</tr>
<tr>
<td>Median age start symptoms in years</td>
<td>3.0 (IQR 0.5 - 4.0)</td>
<td>3.0 (IQR 0.0 - 4.0)</td>
<td>0.962</td>
</tr>
<tr>
<td>Median 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>0.025*</td>
</tr>
<tr>
<td>Treated by general practitioner only</td>
<td>58 (34%)</td>
<td>26 (37%)</td>
<td>0.295</td>
</tr>
<tr>
<td>Use of psychopharmac</td>
<td>0 (0%)</td>
<td>5 (7%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Previously diagnosed with ASD</td>
<td>0 (0%)</td>
<td>13 (19%)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*ASD = Autism Spectrum Disorder; SRS = Social Responsiveness Scale; SCQ-L = Social Communication Questionnaire-Lifetime; IQR = Inter Quartile Range; FC = Functional Constipation; FI = Fecal Incontinence; FNRFI = Functional Non- Retentive Fecal Incontinence; * = statistically significant*
duration of symptoms than children without ASD symptoms (5.5 vs. 4.5 yrs, \(U=4423; z=-2.25; p=0.025\)). The median age at onset of symptoms of a FDD was 3.0 years in both children with and without ASD symptoms.

**Discussion**

This is the first prospective study assessing the prevalence of ASD symptoms in children presenting with either functional constipation or functional non-retentive fecal incontinence. In these children referred to a specialized outpatient clinic, a strikingly high prevalence of 29% of concomitant ASD symptoms was found. Of all 242 patients, 5.4% had already been diagnosed with ASD, which is remarkably higher than the prevalence of ASD in the general population. Children with ASD symptoms were older at presentation at our outpatient clinic and had experienced FDD symptoms for a longer time. There were no other clinical characteristics that significantly differed between children with and without ASD symptoms.

Our results are in line with the retrospective study by Pang et al. describing a high prevalence (8.5%) of ASD diagnoses in children with FC.\(^\text{16}\) Furthermore, the current study underlines the presence of a co-occurrence of FDD and ASD as previously described in children with ASD. The prevalence of constipation in children with ASD has been reported to range from 20% to 33.9% according to recent studies using parent reports or medical charts.\(^\text{8,9,11,24}\) Afzal et al. showed that fecal loading and a megarectum upon an abdominal X-ray were more common among children with ASD compared to controls (54 vs. 24%, resp.).\(^\text{7}\) Furthermore, a recent study reported that of all gastrointestinal disorders present in ASD children, constipation is the most commonly found entity (85%).\(^\text{10}\)

There are several factors that could contribute to the co-occurrence of FDD and ASD (symptoms) in children. FDD and ASD are both heterogeneous disorders in which genetic factors likely play a role.\(^\text{5,25}\) The association of FDD and ASD (symptoms) could therefore be explained by the presence of contiguous gene syndromes resulting from mutations in multiple adjacent genes yet to be discovered that are associated with both disorders.\(^\text{26}\) Furthermore, FDD could be associated with atypical sensory processing, difficulties in making sense of sensory stimuli, or motor problems frequently observed in ASD and thereby disturbed gastrointestinal motility and defecation physiology.\(^\text{27-29}\) Also, it can be hypothesized that children with ASD (symptoms) ignore their urge to defecate as they can be extremely focused on other matters in their environment.

FDD might as well be secondary to behavioral problems in children with (symptoms of) ASD, their resistance to change and difficulties in acquiring new skills, complicating the toilet training period which is known to be a possibly critical phase in the development of FDD.\(^\text{30}\) It has been hypothesized that a period of an inflammatory gastrointestinal process, enterocolitis, is associated with the onset of ASD. However, in a study by Sandhu
et al., there were no symptoms of enterocolitis in the early stool patterns of ASD children to support this hypothesis. Children with ASD often suffer from food selectivity and abnormal feeding habits have commonly been proposed to be associated with FDD in children with ASD. However, dietary habits could not be related to the presence of gastrointestinal problems including constipation in a recent study in ASD children. Lastly, FDD could be a side-effect of drugs used for the treatment of ADHD-like symptoms in ASD patients, such as Methylphenidate, Atomoxetine or Dexamphetamine. However, in this study, only five patients were recorded to use ADHD medication and in all of these patients FDD symptoms had commenced years before starting psychopharmacotherapy.

This study has several strengths. The diagnosis of FC or FNRFI in children was made according to the internationally accepted ROME III criteria by physicians highly experienced in diagnosing and treating FDD in children. Two separate validated ASD screening instruments with high sensitivity and specificity were used to prospectively assess the prevalence of ASD symptoms. In this way, a careful assessment yielded a strikingly high prevalence of ASD symptoms in children presenting with FDD. Nevertheless, there are some important points that should be taken in mind when interpreting our results and extrapolating them to other patient cohorts. Firstly, there might have been a selection bias towards more severe cases of FDD as the recruitment site was a tertiary referral center for children with FDD. This could have resulted in a higher overall prevalence of ASD symptoms as children presenting at our clinic are often difficult to treat. However, more than a third of patients had been referred directly by their GP and had never been treated before by a pediatrician or pediatric gastroenterologist. Moreover, the prevalence of ASD symptoms according to validated ASD screening instruments was similar in children only treated by a GP and children referred by a pediatrician or pediatric gastroenterologist (data not shown).

Secondly, patients were not subjected to an extensive standardized assessment including direct observation and a detailed developmental history, which are mandatory to make an ASD diagnosis. However, the cut off values for the two screening instruments have been validated in the general population and have shown a good correlation with standardized instruments.

Our findings may have large implications for clinical practice as well as research concerning FDD in children. In our study, ASD symptoms according to the validated screening instruments were frequently found to have been overlooked by health care professionals referring the children with FDD. We stress that professionals should be alert for ASD symptoms in children presenting with FDD as the presence of ASD symptoms may give rise to a different therapeutic approach. Apart from age at presentation and a longer duration of symptoms, we found no other clinical characteristics clearly differentiating between children with FDD with and without ASD symptoms. Standard screening of children presenting with FDD for ASD symptoms using standardized instruments which can be followed by referral for further clinical assessment in case abnormal scores are found might therefore be feasible. Future research by means of randomized controlled trials
should further clarify whether children with FDD and co-occurring ASD symptoms would benefit from an adaptation of the current therapeutic strategy for FDD, for instance by adding specialized psycho-educational, psycho-therapeutic or psychiatric care to standard protocols. Clinical research programs on FDD should include ASD screening questionnaires in their protocols as a standard procedure as the presence of ASD symptoms might possibly influence outcomes regarding pathophysiology and treatment response. Future research should focus on unraveling the pathophysiology behind the co-occurrence of FDD and ASD symptoms. Gastrointestinal motility testing in children with FDD with and without ASD symptoms combined with functional MRI studies might lead to more insight in the possibly joint pathophysiology of FDD and ASD.

Conclusions

In this study, a remarkably high prevalence of ASD symptoms was found in children presenting with FDD at a specialized outpatient clinic. Only a small subset of these children had already been diagnosed with ASD. These findings further strengthen the hypothesis of a possible association between FDD and ASD (symptoms) in children. Clinicians and researchers should be aware of ASD symptoms in children with FDD.

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Reference list


