Title: Predictors of Slow Colonic Transit in Children

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Abstract

Purpose Slow transit constipation (STC) and functional faecal retention (FFR) are two forms of severe intractable constipation in childhood diagnosed by nuclear transit studies (NTS). This retrospective study aims to identify the predicting factors for STC and FFR by looking at the association with neuropsychiatric disorders (NPD), obesity, family history of constipation and atopic disease.

Patients and methods A retrospective chart review was conducted on children with intractable constipation referred for NTS between 1st April 2003 and 1st April 2014. Comparisons were made between STC, FFR and normal transit patients with regards to NPD, obesity (BMI z-score >95th percentile), family history of constipation in first and second-degree relatives and atopic disease which included food allergy, asthma and eczema.

Results Between 2003 and 2014, 97 patients were referred for a NTS. Out of 36 patients with NPD, 21 (58.3%) had STC and 13 (36.1%) had FFR ($p <0.05$). 15.8% of patients with constipation were obese, compared to 6.4% in the general Australian paediatric population ($p <0.05$). There was no significant association between constipation and atopic disease or family history.

Conclusion Neuropsychiatric disorders, in particular autism, are useful predictors of STC and FFR in children. Obesity may be associated with a higher risk of developing chronic constipation.

Keywords Constipation. Slow transit constipation. Functional faecal retention. Scintigraphy.
Introduction

Constipation is commonly seen in children, with a reported prevalence in the general population ranging from 0.7% to 29.6% [1]. It is usually managed with the use of laxatives and dietary modifications. Standard laxative therapy consists of a wetting agent, usually polyethylene glycol (PEG) for at least 6 months with variable dose. Constipation non-responsive to medical therapy for ≥ 6 months is defined as intractable [2-4]. In these cases if the constipation is not caused by a known etiology such as Hirschsprung disease or Cow’s milk protein allergy, further investigations are warranted. Nuclear colonic transit studies have been used to assess the nature of constipation and categorize it into slow transit constipation (STC) or functional fecal retention (FFR) by measuring the transit time and distribution of a nuclear tracer through the colon. Slow transit constipation is characterized by delayed passage of fecal matter through the proximal colon whereas functional fecal retention describes delayed transit in the rectosigmoid region only [2].

Nuclear transit studies are now used for the early identification of STC and FFR patients which allows for an efficient management protocol, in particular the use of transcutaneous electrical stimulation therapy which has shown some benefit in STC patients [5]. NTS has proven quite effective in diagnosing constipation, in particular STC, after the wireless motility capsule [6]. However, like other imaging techniques, it is expensive and time-consuming so it would be valuable to establish a set of predicting factors for slow transit that can help select patients to be referred for nuclear transit studies. Childhood constipation has been associated with several disorders in the past, in particular neuropsychiatric disorders and autism spectrum disorders (ASD). In a previous study conducted by the senior author, it was found that 8.5% of patients presenting with severe intractable constipation had ASD, compared with the incidence of ASD in the Australian population of up to 8 per 10,000 [7,8]. Overall 24% of our chronic constipation patients had some form of neuropsychiatric disorder, including ASD. Based on the clinical history, it was suggested that these patients may also suffer from STC. Other factors associated with constipation include obesity, family history of constipation and atopic disease in particularly food allergy [9-11].

This study aims to describe a set of predicting factors for slow transit constipation and functional faecal retention defined by nuclear transit studies. We hypothesize that patients with neuropsychiatric disorders will have a higher occurrence of STC and that obesity will be more prevalent in FFR patients. We also expect to find a positive association between constipation and both family history and atopic disease.

Materials and Methods

A retrospective chart review was conducted on children of specialized paediatric surgical clinic who had a colon transit study for intractable constipation between 1st April 2003 and 1st April 2014. Inclusion criteria for colonic transit study included presence of constipation symptoms for ≥ 2 years with failure of medical therapy, including diet, laxatives and behavioural therapy, for ≥ 6 months [4]. Organic causes were excluded through clinical assessment, cow’s milk exclusion diet, rectal biopsy and other investigation (for instance thyroid function testing) as appropriate. The NTS was used to categorize patients into having either slow transit constipation (STC), functional fecal retention (FFR) or normal transit (N). The transit study was performed by oral administration of a radiopharmaceutical gallium-67 citrate in a standard formula on day 1. Images were collected daily over a 96 hour period and the diagnostic protocol used was similar to that by Shin et al [2]. Normal transit was defined as tracer present in the cecum at 6 hours, in the rectosigmoid colon at 30 hours and undetectable at 48 hours. STC was identified as a colonic transit that was globally delayed with retention of tracer proximal to the rectosigmoid at 48 hours. FFR appears as a normal transit throughout the entire colon with significant tracer hold-up in the rectosigmoid at 48 hours.

Prior to undergoing the NTS, a detailed history was obtained at first presentation. Using patients’ medical records, the following information was obtained and entered into a database; gender, age at onset, age at first presentation, duration of constipation, weight and height at first presentation, meconium delay, soiling, stool frequency and consistency, pre-existing conditions in particular neuropsychiatric disorders (NPD), atopic disease and family history of constipation. The spreadsheet software used was Microsoft Office Excel 2013.
All patients were diagnosed with constipation according to the Rome III criteria: children with at least two of; hard, large-diameter stools, frequency ≤2 stools per week, soiling episodes ≥1 per week, pain on defecation and presence of a large palpable fecal mass in the rectum [12]. Stool type was described according to the Bristol Stool Chart [13]. Atopic diseases included both self-reported and documented eczema, food allergies and asthma. Neuropsychiatric disorders, including autism, were diagnosed either by a clinical psychologist, the patient’s general practitioner or a paediatrician according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM IV) [14]. BMI z-scores and percentiles were obtained using a BMI-percentile-for-age calculator based on growth charts developed by the Center for Disease Control and Prevention [15]. Categories based on percentile were as follows; those in the <5th percentile were classed as underweight, 5 - 85th percentile as healthy, 85 - <95th percentile as overweight and those in the 95th percentile or higher as obese.

The data was analyzed and comparisons were made between the three types of constipation and their associations with the main factors of interest; namely obesity, NPD, meconium delay and atopic disease. Statistical analysis was done using the Fisher’s exact test, the Mann-Whitney $U$ test and the unpaired $t$ test.

**Results**

**General features**

Between 2003 and 2014, 97 patients were referred for a NTS. There were 38 females and 59 males in total, however only 86 out of the 97 patients had accessible and valid NTS reports. There were 3 invalid NTS reports, including two patients who had gastroenteritis and one patient who was on laxatives during the study. The remaining 8 patients’ NTS reports could not be found. Table 1 describes the demographic features of patients distinguished by type of constipation. 39 patients had slow transit constipation, 29 had functional fecal retention and 18 patients had normal transit studies. STC patients had the earliest age of onset at 6 (1-128) months and the longest duration of symptoms at 66 (5-183) months, although both values did not reach statistical significance. With regards to gender, 30 of 35 females (85.7%) had an abnormal NTS report i.e. either STC or FFR compared to 38 of 51 males (74.5%) ($p = 0.283$).

The clinical manifestations of constipation in STC, FFR and N patients are described in Table 2. All patients were on laxatives at the time of first presentation. There were no significant differences in stool type, stool frequency or soiling patterns. Only 48 patients’ meconium history was known and recorded.10 patients had a known history of delayed passage of meconium at birth and 9 of these patients showed an abnormal NTS ($p = 0.41$). It would require 30 meconium delay patients to prove a significant result. Meconium delay was most common in STC patients (35.3%), followed by FFR (15.8%) and least common in N patients (8.3%).

**Neuropsychiatric disorders**

The occurrence of neuropsychiatric disorders among STC, FFR and normal patients are represented in Table 3. 35 patients were shown to have history of a neuropsychiatric disorder and a valid NTS report; including attention deficit hyperactivity disorder (ADHD) and/or autism spectrum disorder (ASD) (19), anxiety (1), cerebral palsy (2), other developmental delay i.e. intellectual, speech and/or motor (11), Sotos syndrome (1), and syringomyelia (1).
When compared to constipated patients with a normal transit study, there is a significantly higher presence of neuropsychiatric disorders in patients with STC or FFR. When STC patients were compared with FFR, there was no significant difference in NPD prevalence. The median age of onset of constipation in NPD patients was 19.5 (1-148) months, which was slightly, but not significantly, higher than in non-NPD patients at 12 (1-128) months ($p = 0.07$).

**Obesity**

The BMI-percentile-for-age calculator showed that STC patients had a mean BMI z-score of 0.238 ($\pm 1.36$) which was very similar to that in FFR patients at 0.241 ($\pm 1.4$). On average, patients with a normal NTS had a z-score of 0.45 ($\pm 1.18$) which is slightly larger than those with an abnormal study but did not attain statistical significance. Among the 76 patients of whom height and weight were recorded at first presentation; 8 (10.5%) were underweight, 47 (61.8%) were healthy, 9 (11.8%) were overweight and 12 (15.8%) were obese. Table 4 shows a comparison of the prevalence of obesity in these constipated patients compared to that of general Australian children in a study by Scott et al which reports a prevalence of 6.4% [16]. The prevalence of obesity is significantly higher in this cohort of constipated paediatric patients than that in the general population studied by Scott et al.

**Atopic disease and family history of constipation**

Out of 90 constipation patients whose atopic or non-atopic history is known and who had a valid NTS report, 31 had some form of atopic disease and 47 had no history of atopy. Among the atopic patients, 27 (87%) had an abnormal NTS while 36 of the non-atopic patients (76%) had a similar result. This difference was not statistically significant ($p = 0.38$).

Family history information was thoroughly obtained from 92 of the constipation patients. 29 patients (31.5%) had a family history of constipation; 20 involving at least one first-degree relative and 9 involving at least one second-degree relative only. There were no significant differences between normal and abnormal studies. However, among the 16 patients with a first-degree family history of constipation and a valid NTS, 10 had STC compared to 3 with FFR ($p = 0.0987$).

**Predictors of Slow Transit Constipation**

There is a trend for constipation patients with STC and FFR as opposed to N transit, to present with multiple predictors, which have shown an association with abnormal transit (Figure 1). 13 (72%) N transit patients presented with $\leq 1$ of the following predicting factors: NPD, atopy, meconium delay and a family history of constipation, with no N transit patients having 3 or 4 of the predicting factors. 17 (43%) STC and 10 (34%) FRR reported $\geq 2$ predictors, but these were not statistically significant compared to N ($p=0.38$ and $p=0.75$).

**Discussion**

Constipation is a common symptom in children and has a variety of etiological factors, thought to include diet and allergies amongst others [1,11]. Severe constipation which cannot be relieved by conventional therapy such as use of laxatives and dietary therapy and does not have a proven organic cause like Hirschprung disease, can be classified using a colonic nuclear transit study (NTS) into slow transit constipation (STC), functional fecal retention (FFR) and normal transit constipation [2]. This study shows that although the general features of constipation are similar
among the three groups, there are a few important factors that may assist in predicting STC and FFR and hence decide which patients to refer for NTS.

Firstly, patients identified with STC and FFR were more likely to have an earlier age of onset (less than 1 year) while in normal transit patients it was at 2 years of age, as shown in table 1. Although this result did not reach statistical significance, likely due to the small sample population, it is worth noting that Shin et al observed similar findings. Shin’s observation is consistent with normal transit constipation patients having acquired and often behavioural causes for their problem [2].

The earliest onset of symptoms is represented by meconium delay, 90% of patients with meconium delay had either STC or FFR, as in table 2. The lack of statistical significance is due to the fact that more than half of the patients’ parents did not know or could not remember when their child passed meconium. However, other studies support our findings and show that a meconium delay of more than 24 hours after birth can be a useful predictor of slow transit constipation [3,17]. Since STC patients had the earliest age of onset and greatest prevalence of meconium delay, it suggests that the underlying etiology for this disorder is an intrinsic gut problem present at birth.

Interestingly, the majority of patients in this study had a stool frequency of greater than 2 per week across all types of constipation, as in table 2, but this may have been due to the laxative effect as some patients were on very high doses. We expected that STC patients would have soft stools while FFR patients would present with harder, less frequent stools yet our results showed no significant difference [2].

Furthermore, our data showed that there was a higher proportion of females with an abnormal NTS than males, although this did not reach statistical significance (Table 1). Previous studies have not reported a gender difference in STC between girls and boys, however Yik et al showed that girls with STC were twice as likely to have reduced substance P in nerve fibres of circular muscle as boys. Interestingly, at puberty the pattern was reversed and the proportion of boys with reduced substance P outweighed that in girls [18]. The literature has established that slow transit constipation in adults is a condition that mainly affects young women [19,20]. Further follow-up is required to determine whether girls with STC are more likely to have the condition later in adulthood.

In a previous retrospective study we conducted on a subset of this data, we showed that a significant proportion of constipated patients suffered from autism and other neurodevelopmental-psychiatric deficits[8]. In fact there was a 100-fold increase in the incidence of ASD compared to the general Australian population [7]. The current results add to this by demonstrating that constipated patients with neuropsychiatric disorders are more likely to have both STC and FFR, as opposed to normal transit (Table 3), even though our original idea was that autism spectrum disorders would be more likely associated with slow transit alone. Several theories have been proposed that could explain the link between autism or neuropsychiatric disorders and constipation.

Neuropsychiatric disorders are primarily diseases of the central nervous system on a broad scale and hence an association with gut pathologies may not be implausible, particularly those involving the enteric nervous system. Recently, a new school of thought has emerged describing the gut-brain-axis and its relationship with autism. Inflammatory processes within the gut, as a result of altered microbiota or food allergens, can cause neuronal damage to the local enteric nervous system, which may manifest as a gastrointestinal disturbance. The idea is that some of the inflammatory mediators involved can cross the blood brain barrier and alter neuronal homeostasis leading to autism [21]. This study found a slightly elevated number of STC and FFR cases in constipated patients with atopic disease. However, there was no association found between atopic disease and neuropsychiatric disorders. Yik et al suggested that food allergies were associated with rapid proximal colonic transit and rectosigmoid hold-up on NTS (suggestive of FFR) in patients with intractable constipation [4]. They also reported a high incidence of anal fissures in these patients which is commonly seen in other atopy-related constipation, namely cow’s milk allergy [22].

The final factor we found to be associated with constipation was obesity. We hypothesized that STC patients would be smaller than FFR patients, however there appeared to be no difference with regards to BMI z-scores. Interestingly, however, patients with normal transit constipation had a two-fold higher z-score than patients with STC or FFR. Furthermore, and significantly, 15.8% of patients with chronic constipation were found to be obese,
compared to 6.4% in the general Australian paediatric population (Table 4). This is consistent with a study by Pashankar et al which showed a 22.4% prevalence of obesity in constipated children compared to 11.7% in control children [9]. Fishman et al looked at the opposite angle and found that out of 80 obese paediatric patients, 23% had constipation and 15% had fecal soiling [23]. Obese patients are more likely to have an unbalanced dietary regimen that may be skewed towards high-fat foods and contain less than the required amount of fiber. Also, obesity has been well-correlated with low physical activity which may be exacerbating the constipation. Huang et al showed a link between constipation and insufficient activity in Chinese adolescents [24]. These findings suggest that obesity and constipation are linked mainly due to lifestyle determinants, rather than intrinsic gut problems related to STC or FFR.

Transcutaneous electrical stimulation therapy has been shown to be beneficial to the management of STC [5]. NTS are required to diagnose STC in chronically constipated patients and hence determine who is suitable for treatment. However NTS are an expensive and time-consuming investigation and determining who is likely to have STC through good clinical predictors can reduce negative results. Studies have shown that 40% of chronic constipation patients investigated with NTS have normal colonic transit [25,26]. Identifying these patients prior to NTS has the potential to make NTS obsolete. Demonstrated in Figure 1, is a descending trend of occurrence of predictors in patients with N transit, with all N patients having <2 predictors. However due to the small sample size the trend is not significant and predictors of STC appear to also be predictors of other abnormal transit, such as FFR. Further study on identifying specific predictors of STC is required to formulate an appropriate diagnostic model.

Conclusion

Slow transit constipation and functional fecal retention are forms of severe chronic intractable constipation that may not be easily diagnosed in children without a nuclear transit study. Accurate diagnosis should lead to efficient treatment. We have shown that several factors may be useful in predicting STC and targeting investigation, the most significant of which are neuropsychiatric disorders including autism. Atopic disease, family history of constipation and delayed passage of meconium may also predict an abnormal study. The prevalence of obesity was also found to be higher in the constipated paediatric population, particularly in patients with normal colonic transit.

References

Table 1  Demographic feature of patients with STC, FFR or normal transit constipation

<table>
<thead>
<tr>
<th></th>
<th>STC (n = 39)</th>
<th>P value (vs N)</th>
<th>FFR (n = 29)</th>
<th>P value (vs N)</th>
<th>N (n = 18)</th>
<th>Total (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>24 (1-128)</td>
<td>NS P = 0.17</td>
<td>14 (1-148)</td>
<td>NS</td>
<td>13 (1-126)</td>
<td>51</td>
</tr>
<tr>
<td>Female</td>
<td>15 (1-128)</td>
<td>NS</td>
<td>13 (1-148)</td>
<td>NS</td>
<td>5 (1-128)</td>
<td>35</td>
</tr>
<tr>
<td>Age at onset (months)</td>
<td>71 (2-154)</td>
<td>NS</td>
<td>60 (8-154)</td>
<td>NS</td>
<td>68.5 (14-144)</td>
<td>65 (2-154)</td>
</tr>
<tr>
<td>Duration of symptoms (months)</td>
<td>66 (5-183)</td>
<td>NS</td>
<td>52 (17-180)</td>
<td>NS</td>
<td>50 (16-144)</td>
<td>61 (5-183)</td>
</tr>
</tbody>
</table>

Age and duration are reported as median data

STC slow transit constipation, FFR functional fecal retention, N normal

Table 2  Clinical presentation details of STC, FFR and normal patients

<table>
<thead>
<tr>
<th></th>
<th>STC (%)</th>
<th>P value (vs N)</th>
<th>FFR (%)</th>
<th>P value (vs N)</th>
<th>N (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool type (1-3)</td>
<td>10 (31.3)</td>
<td>NS</td>
<td>13 (44.8)</td>
<td>NS</td>
<td>7 (43.8)</td>
<td>30 (39)</td>
</tr>
<tr>
<td>Stool type (4-7)</td>
<td>22 (68.7)</td>
<td>NS</td>
<td>16 (55.2)</td>
<td>NS</td>
<td>9 (56.2)</td>
<td>47 (61)</td>
</tr>
<tr>
<td>Stool frequency</td>
<td>10 (30.3)</td>
<td>NS</td>
<td>10 (35.7)</td>
<td>NS</td>
<td>5 (29.4)</td>
<td>25 (32.1)</td>
</tr>
<tr>
<td>≤2 per week</td>
<td>23 (69.7)</td>
<td>NS</td>
<td>18 (64.3)</td>
<td>NS</td>
<td>12 (70.6)</td>
<td>53 (67.9)</td>
</tr>
<tr>
<td>≥2 per week</td>
<td>29 (90.6)</td>
<td>NS</td>
<td>21 (75)</td>
<td>NS</td>
<td>15 (83.3)</td>
<td>65 (83.3)</td>
</tr>
<tr>
<td>Soiling</td>
<td>6/17 (35.3)</td>
<td>NS p = 0.18</td>
<td>3/19 (15.8)</td>
<td>NS</td>
<td>1/12 (8.3)</td>
<td>10 (20.8)</td>
</tr>
</tbody>
</table>

P values calculated with Fisher’s exact test.
*Meconium delay percentages only represent patients of whom meconium delay status is known.

Table 3  Comparison of neuropsychiatric disorder presence in STC, FFR and normal patients

<table>
<thead>
<tr>
<th></th>
<th>STC</th>
<th>P value (vs N)</th>
<th>FFR</th>
<th>P value (vs N)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPD (n = 36)</td>
<td>21</td>
<td>P = 0.003</td>
<td>13</td>
<td>P = 0.02</td>
<td>2</td>
</tr>
<tr>
<td>Non-NPD (n = 49)</td>
<td>18</td>
<td></td>
<td>16</td>
<td></td>
<td>15</td>
</tr>
</tbody>
</table>

P values calculated with Fisher’s exact test.

NPD Neuropsychiatric disorder, Non-NPD Non-neuropsychiatric disorder
Table 4 Contingency table comparing obesity prevalence in constipated patients against that in general Australian children.

<table>
<thead>
<tr>
<th></th>
<th>Australian children (%)</th>
<th>Australian children presenting with constipation in current study (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese</td>
<td>133 (6.4%)</td>
<td>12 (15.8%)</td>
<td>P = 0.00416</td>
</tr>
<tr>
<td>Non-obese</td>
<td>1933 (93.6%)</td>
<td>64 (84.2%)</td>
<td></td>
</tr>
</tbody>
</table>

P values calculated with Fisher’s exact test.

Figure 1 Number of predicting factors for STC in constipation patients