Constipation in Duchenne Muscular Dystrophy: Prevalence, Diagnosis, and Treatment

Dror Kraus, MD, PhD1, Brenda L. Wong, MD1, Paul S. Horn, PhD1, and Ajay Kaul, MD2

Objectives To determine the prevalence and clinical characteristics of constipation among patients with Duchenne muscular dystrophy (DMD).

Study design This cross-sectional prospective study included 120 patients (age range 5-30 years old) with an established diagnosis of DMD. Participants filled out the constipation section of a validated Questionnaire on Pediatric Gastrointestinal Symptoms based on Rome-III Criteria (QPGS-RIII) for the diagnosis of functional constipation as part of a routine clinic visit. We evaluated several potential screening methods for constipation: the Bristol stool form scale, routine physical examination, and fecal load on abdominal radiograph. These methods were compared with the QPGS-RIII in diagnosing functional constipation. Risk factors for the development of functional constipation were determined.

Results Based on the QPGS-RIII, 46.7% of patients with DMD in this cohort were diagnosed with functional constipation. Prevalence was not affected by age or functional status. None of the screening methods tested were sensitive enough to diagnose functional constipation. Among patients with constipation, only 43.6% received specific treatment for constipation and only one-half of these treated patients reported resolution of constipation.

Conclusions This study systematically examined constipation among patients with DMD and provides evidence that constipation among patients with DMD is highly prevalent, underdiagnosed, and undertreated. QPGS-RIII is easy to administer and is an efficient tool to diagnose functional constipation in patients with DMD in a clinic setting. (J Pediatr 2016;■■■■■).

Duchenne muscular dystrophy (DMD) is an X-linked degenerative muscle disorder characterized by progressive weakness affecting skeletal and cardiac muscle. Multidisciplinary supportive care has led to a significant increase in both life expectancy and quality of life of patients with DMD but has revealed a new array of associated medical challenges.1-3 The involvement of the gastrointestinal (GI) tract is one of the emerging foci of interest in DMD management.4-6 GI symptoms are diverse and include decreased masticatory performance,7,8 dysphagia,9,10 gastric hypomotility,11 and constipation.

Constipation is a common clinical observation in patients with DMD.12 In a study of 118 patients that focused on feeding problems and weight gain in DMD, 36% of patients reported constipation.6 For comparison, the prevalence of constipation in the pediatric and young adult population ranges from 6%-15%.13-17 Despite its prevalence, clinical characteristics of constipation in patients with DMD have not been systematically investigated.

Our center has provided interdisciplinary care to patients with DMD since 2000. As part of standard care, we have systematically gathered information regarding clinical status, GI symptoms, and nutrition. The aim of this study was to determine the prevalence of functional constipation, to identify possible risk factors, and to evaluate effectiveness of different screening methods to diagnose constipation in a cohort of established patients with DMD. We hypothesized that patients with DMD would have a higher prevalence of constipation than the general population and that prevalence will increase with age and with worsening functional status. We further hypothesized that clinical constipation will be underreported by patients and underdiagnosed by caregivers.

Methods

This prospective cross-sectional study included a cohort of patients with DMD seen at the comprehensive neuromuscular center at Cincinnati Children’s Hospital Medical Center between May 2013 and August 2014. Patients were invited to participate in the study during a routine follow-up visit. The study was approved by the local institutional review board.

Inclusion criteria were a diagnosis of DMD based on clinical presentation and verified by lack of dystrophin on muscle biopsy or known dystrophin

| BSFS  | Bristol stool form scale |
| DMD   | Duchenne muscular dystrophy |
| GI    | Gastrointestinal |
| QPGS-RIII | Questionnaire on Pediatric Gastrointestinal Symptoms based on Rome-III Criteria |
gene mutation and age >5 years old. There were no exclusion criteria. Written consent/assent to participate in the study was obtained from the parents and/or the patient, based on age and legal power-of-attorney status.

All patients were evaluated for constipation section C (constipation) of the Questionnaire on Pediatric Gastrointestinal Symptoms based on Rome-III Criteria (QPGS-RIII), a diagnostic tool that has been validated in children and is widely accepted for both clinical and research purposes.\textsuperscript{18-20} We used the parent-report version for all participants younger than 18 years of age. This questionnaire consists of 11 items regarding frequency and severity of constipation symptoms over the 2 months prior to the visit. Per Rome-III criteria, constipation was diagnosed based on receiving 2 or more positive answers and after ruling out irritable bowel syndrome using section B of the QPGS-RIII questionnaire. Patients over 18 years old used questionnaires for adults, which were scored based on the Rome-III diagnostic criteria for functional GI disorders.\textsuperscript{21}

In addition, all patients were evaluated for constipation by: (1) Bristol stool form scale (BSFS): patients or their parents were asked to identify a typical stool form, with stool type-1 or type-2 considered to represent constipation\textsuperscript{19,22}; (2) fecal load assessment by a pediatric gastroenterologist, who examined spine radiographs, which were done for clinical monitoring of steroid-induced vertebral fractures, and graded as normal or mildly, moderately, or severely increased; and (3) abdominal examination to determine presence and location of fecal masses, abdominal tenderness, fullness, or other abnormal findings (rectal examination was deferred unless clinically indicated). Additional data included demographics; genetic mutation (if known); Functional Mobility Scale\textsuperscript{23}; North Star Ambulatory Assessment (for ambulatory patients)\textsuperscript{24,25}; ambulatory status (ambulatory vs nonambulatory); medications (glucocorticoid treatment, constipation treatments, other medications); and an estimate of fiber, fluid, and dietary calcium intake was used in 54.9% of patients in this study.

Participants were diagnosed as having constipation if they fulfilled Rome-III criteria for functional constipation (based on the QPGS-RIII) or if there was prior documentation of constipation and the patients were treated for constipation status. Calcium supplementation for those with suboptimal dietary calcium intake was used in 54.9% of patients in this study.

Data Analyses
Descriptive statistics were used to calculate the prevalence of constipation in this cohort. Logistic regression with backward elimination variable selection was used to determine possible predictors of constipation.

### Results

The study enrolled 120 patients with DMD (mean age 13 ± 5.2 years, range 5-30 years). Twenty-five patients were over 18 years old (mean age 21.3 ± 3.3 years). Patient characteristics are described in Table I.

#### Prevalence of Constipation

The overall prevalence of constipation was 46.7% (56 out of 120). The prevalence among patients younger than 18 years of age was slightly lower than in patients older than 18, although this difference did not reach statistical significance (44.8% vs 52%, \( P = .65 \)). No differences were found when comparing patients below and above 10 years of age (\( P = .83 \), data not shown). Similarly, the proportion of patients/families that raised concerns regarding constipation did not differ between patients younger and older than 18 years of age (Table II).

#### Risk Factors for Constipation

We evaluated the clinical characteristics of this cohort in an attempt to identify risk factors for the development of constipation. Response rates for all variables were >85%.

Functional status was assessed using the North Star Ambulatory Assessment, the Functional Mobility Scale, and ambulation status (ambulatory vs nonambulatory). We presumed that lack of ambulation may be a contributing factor for constipation, but none of these measures was associated with the presence of constipation (\( P = .54, .68, \) and 1.0, respectively). We evaluated calcium supplementation and glucocorticoid treatment as possible risk modifiers. Calcium supplementation could potentially increase the risk of constipation and glucocorticoid treatment could be associated with a decreased risk secondary to improved functional status. Calcium supplementation for those with suboptimal dietary calcium intake was used in 54.9% of patients in this study.

### Table I. Patient characteristics of a cohort of 120 patients with DMD

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Age &lt;18 y</th>
<th>Age &gt;18 y</th>
<th>Total</th>
<th>( P ) value (&lt;18 y vs &gt;18 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants (% of total)</td>
<td>95 (79.2)</td>
<td>25 (20.8)</td>
<td>120</td>
<td>n/a</td>
</tr>
<tr>
<td>Age in y (average ± SD)</td>
<td>10.8 ± 2.8</td>
<td>21.3 ± 3.3</td>
<td>12.9 ± 5.2</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Age range in y</td>
<td>5-17</td>
<td>18-30</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Ambulatory (%)</td>
<td>80 (64.2)</td>
<td>5 (20)</td>
<td>85 (70.8)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>North Star Ambulatory Assessment (average ± SD)</td>
<td>21.6 ± 8.1</td>
<td>n/a</td>
<td>21.3 ± 8.1</td>
<td>-</td>
</tr>
<tr>
<td>Functional Mobility Scale</td>
<td>2.33 ± 1.6</td>
<td>5.44 ± 1.87</td>
<td>2.98 ± 2.08</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Steroid treatment (%)</td>
<td>91 (95.7)</td>
<td>21 (84)</td>
<td>112 (91.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium supplementation (%)</td>
<td>51 (56)</td>
<td>15 (60)</td>
<td>66 (56.9)</td>
<td>NS</td>
</tr>
</tbody>
</table>

n/a, not applicable; NS, not significant.
cohort, and 91.8% of patients were on long-term glucocorticoid therapy. Neither of these treatments had a significant effect on the prevalence of constipation ($P = .36$ and $P = .45$ for treated vs untreated participants, respectively).

A logistic regression analysis with backward elimination variable selection failed to identify any combination of factors that could reliably predict the presence of constipation.

### Analysis of Individual QPGS-RIII Criteria

Focusing on the components of the pediatric Rome-III criteria (for patients <18 years old) for functional constipation, common symptoms were a history of straining (53.1%) and presence of pain with defecation (27.8%). Other symptoms (>20% positive responses) included the need to rush to the restroom (25.8%), tenesmus (24.7%), and clogging the toilet (22.6%). The symptoms “traditionally” associated with constipation (ie, bowel movement frequency of twice weekly or less and hard stool consistency) occurred in only 16% and 17%, respectively.

Among individual diagnostic criteria, the presence of pain with defecation had reasonable specificity of 87.5% for the presence of constipation, but had low sensitivity, 61.9%. Similarly, a history of stool clogging the toilet had good specificity of 98.2%, but a low sensitivity of 54.8%. Further analysis included logistic regression with the diagnosis of constipation as the response. Backward elimination variable selection was used on the Rome-III subcomponents along with the variables fiber intake, fluid intake, and parental concern. The presence of pain, a history of toilet clogging, and parental concern were retained in the model (area under the receiver operating characteristic curve of 0.91).

The logistic regression shows the presence of at least 1 of these 3 factors increases the odds of constipation. However, because of their relatively low sensitivities, none of these factors, alone, or in combination, could serve as a reliable screening method for constipation in this cohort.

### Evaluation of Potential Screening Methods

Presence of patient/caregiver concern correctly identified only 50% of patients, who fulfilled criteria for constipation, underlining the need for alternative screening methods. We, therefore, evaluated several potential modalities and compared their performance against the QPGS-RIII as a reference. The purpose of these comparisons was to identify a screening method that could be quicker and be able to identify most children with functional constipation. The sensitivity, specificity, and positive and negative predictive values of the potential screening methods compared with the QPGS-RII are given in Table III.

Constipation may generate abnormal findings on physical examination. About one-quarter of patients in this cohort (28 patients) had at least 1 abnormal finding associated with constipation on physical examination of the abdomen. The most common abnormal finding was abdominal fullness or distension (24 patients). Four patients had hyperactive bowel sounds, and 3 patients had palpable fecal masses. The presence of any abnormal finding on exam was quite specific (83.8%), but had a low sensitivity of 34.8%.

The BSFS was developed as a research tool to assess GI transit times and constipation. In the current cohort, the BSFS had a low sensitivity of 18% and a specificity of 95% when using either stool form 1 or 2 as indicative of presence

### Table II. Prevalence of constipation and of associated abnormal findings (on history, physical examination, or abdominal radiograph) during a routine clinic visit

<table>
<thead>
<tr>
<th>Definition of constipation/abnormal finding</th>
<th>Age &lt;18 y (n = 95)</th>
<th>Age &gt;18 y (n = 25)</th>
<th>Total</th>
<th>$P$ value &lt;18 y vs &gt;18 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation per Rome-III criteria</td>
<td>39 (41.0%)</td>
<td>11 (44.0%)</td>
<td>50 (41.7%)</td>
<td>.79</td>
</tr>
<tr>
<td>Constipation per Rome-III criteria OR asymptomatic on treatment for constipation</td>
<td>43 (45.2%)</td>
<td>13 (52.0%)</td>
<td>56 (46.7%)</td>
<td>.54</td>
</tr>
<tr>
<td>Constipation as patient concern</td>
<td>28 (30.1%)</td>
<td>5 (20%)</td>
<td>33 (27.5%)</td>
<td>.45*</td>
</tr>
<tr>
<td>Receiving treatment for constipation</td>
<td>20 (21.0%)</td>
<td>4 (16%)</td>
<td>24 (20%)</td>
<td>.78*</td>
</tr>
<tr>
<td>Abnormal abdominal examination</td>
<td>22 (23.4%)</td>
<td>6 (30%)</td>
<td>28 (23.3%)</td>
<td>.50</td>
</tr>
<tr>
<td>Large stool load on abdominal radiograph</td>
<td>29 (31.2%)</td>
<td>3 (13.0%)</td>
<td>32 (27.6%)</td>
<td>.11*</td>
</tr>
</tbody>
</table>

*Fisher exact test was used instead of $\chi^2$ test.

### Table III. Comparison of possible screening methods for constipation compared with the Rome-III criteria in 120 patients with DMD

<table>
<thead>
<tr>
<th>Screening method</th>
<th>n positive</th>
<th>Specificity (%)</th>
<th>Sensitivity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rome-III criteria</td>
<td>50</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Examination</td>
<td>28</td>
<td>83.8</td>
<td>34.8</td>
<td>59.3</td>
<td>65.6</td>
</tr>
<tr>
<td>Abdominal plain film - large stool load</td>
<td>32</td>
<td>68.7</td>
<td>22.4</td>
<td>34.4</td>
<td>54.8</td>
</tr>
<tr>
<td>Bristol stool chart score ≥2</td>
<td>12</td>
<td>94.6</td>
<td>18</td>
<td>75</td>
<td>55.9</td>
</tr>
<tr>
<td>Bristol stool chart score ≤3</td>
<td>50</td>
<td>63.6</td>
<td>60</td>
<td>60</td>
<td>63.6</td>
</tr>
<tr>
<td>Previous diagnosis of constipation</td>
<td>34</td>
<td>83.9</td>
<td>66.7</td>
<td>75.7</td>
<td>77.1</td>
</tr>
<tr>
<td>Constipation as parental/patient concern</td>
<td>33</td>
<td>86.8</td>
<td>50</td>
<td>72.7</td>
<td>71.1</td>
</tr>
</tbody>
</table>

*Abnormalities on examination: fullness, distension, tenderness, palpable masses, or abnormal bowel sounds.
†Data includes only patients <18 y old.
of constipation. Inclusion of type-3 stools as indicative of constipation increased the sensitivity to 60%, but decreased the specificity to 63.6%. Routine abdominal radiograph for assessment of fecal load had a low sensitivity of 22.4% and did not reliably predict the presence of constipation.

**Symptomatic Treatment for Constipation**

A survey of symptomatic treatments for constipation revealed several unexpected findings. Of 56 patients that fulfilled criteria for constipation, only 24 patients (43.6%) received treatment for constipation (Figure). Twenty-three of the 24 patients received polyethylene glycol 3350; one patient received a compound consisting of sodium picosulfate, magnesium oxide, and anhydrous citric acid. In the treated group, 13 patients (54.1%) were still constipated according to Rome-III criteria, even after correction for patients, whose positive result on the questionnaire was due to a previous diagnosis of constipation.

**Discussion**

This cross-sectional, prospective study focused on clinical characteristics of constipation in a large cohort of patients with DMD.

Almost one-half (46.7%) of patients in this cohort met criteria for functional constipation. Not only is this prevalence higher than previous estimates, it highlights the need for a standardized approach toward diagnosis of constipation in patients with DMD.

Our analysis failed to identify any combination of clinical factors that could reliably predict the presence of constipation among patients with DMD. In particular, the prevalence of constipation in patients with DMD did not significantly increase with age or with worse functional status. This finding was contrary to the previous report by Pane et al and to our own hypothesis. Hence, constipation in DMD is unlikely to be related to an ineffective bear-down (Valsalva) maneuver or prolonged immobility alone.

Similarly, our results argue against a progressive dysfunction of GI smooth muscle. This notion is supported by findings of Korman et al, who demonstrated normal oro-cecal transit times in 10 patients with DMD. Of note, this was one of only 2 studies published on GI transit times in DMD. The second, which can be viewed as complementing the previous one, investigated colonic rather than oro-cecal transit times. Interestingly, it showed prolonged colonic transit times in 7 of 12 patients with DMD, arguing for an inherent motility defect in these patients. Both studies were small, carried out in the 1990s (prior to standard use of chronic glucocorticoid treatment), and reached somewhat contradictory results with regards to smooth muscle function in patients with DMD. We conclude that there is a significant knowledge gap regarding GI motility in DMD and additional physiological studies are warranted.

This study confirmed our hypothesis that constipation among patients with DMD is underreported and undertreated. The QPGS-RIII revealed that a significant proportion of patients and families failed to report or to recognize symptoms of clinical constipation. Parental concern expressed as part of a standard intake questionnaire was clearly associated with a diagnosis of constipation but failed to identify one-third of symptomatic patients. This finding may be related to the fact that constipation is more commonly identified as either infrequent bowel movements or hard stools. In fact, these 2 criteria combined accounted for only 17% of diagnoses of constipation among patients younger than 18 years old. The more detailed inquiry about pain, straining, stool caliber, and tenesmus significantly improved the correct identification of symptomatic patients. Taken together, the high prevalence of constipation and tendency to underreport it, highlight the need to increase awareness about constipation among both families and providers.

Compared with the QPGS-RIII, the BSFS lacked sensitivity and was comparable in performance to inquiring about patient/family concerns regarding constipation. Physical examination and abdominal radiographs were not sensitive enough to identify constipation either and could not be relied upon as a sole diagnostic tool for diagnosing constipation. The low sensitivity of the abdominal examination may have been in part due to the fatty abdominal wall found in a majority of patients. In the context of constipation, this examination, particularly abdominal tenderness and presence of palpable fecal masses, should raise concern for severe constipation and, therefore, prompt the consideration of more aggressive symptomatic treatment to avoid fecal impaction.

The QPGS-RIII was easy to administer in this population and took ~5 minutes to complete. It provided important data that allowed the healthcare provider to address constipation as part of a multidisciplinary treatment plan. In our experience, it seems well suited for use in the setting of a routine outpatient visit and provides more useful information than any of the other screening methods we tested.
An important limitation of the QPGS-RIII in this study related to patients who were being treated for constipation. In patients whose constipation was diagnosed and treated, inclusion of item 10 in the QPGS-RIII (presence of a prior presence of large stool load) occasionally led to a false impression of undertreatment (ie, persistent constipation despite treatment). A subset analysis of patients on symptomatic treatment for constipation identified 6 patients, whose diagnosis of persistent constipation was dependent on a positive response to item 10 in the QPGS-RIII. In our analysis, these patients were reclassified as being successfully treated. These patients are indeed at increased risk of recurrence of constipation symptoms and should be treated and monitored accordingly. However, one should note this shortcoming of the QPGS-RIII when assessing the effect of an intervention aimed to treat constipation. We believe this limitation to be applicable to all children assessed by this questionnaire, regardless of their medical background or presumed cause of constipation.

A significant proportion of patients with constipation remained symptomatic despite ongoing treatment, even after the above-mentioned adjustment of the diagnostic criteria. The management of constipation in patients with DMD is essentially similar to patients without DMD. It includes increased fluid intake, dietary modifications, and treatment with polyethylene glycol 3350.29 As many patients with DMD are seen in multidisciplinary clinics at relatively long intervals, effective treatment of constipation depends on detailed communication of the management plan to the patient/family and to the patient’s primary care provider. As most pediatricians and primary care providers are familiar with managing constipation, their involvement would likely be associated with a better outcome in these patients.

This study has several limitations. The cross-sectional design of this study did not permit longitudinal evaluation of constipation in this cohort to show the impact of systematic evaluation on clinical outcomes. Similarly, we were not able to evaluate different strategies of treating constipation in this cohort. Despite the lack of longitudinal data to address these knowledge gaps, our findings support the need for early recognition and proactive management of constipation in patients with DMD.

We believe this study has several pertinent and clinically meaningful applications. Because of the relatively large sample size, it provided reliable data regarding prevalence and clinical characteristics of constipation in a cohort of patients with DMD. It highlighted the need for increased awareness regarding constipation in patients with DMD among both caregivers and healthcare providers. This seems to hold true for patients of all ages and all functional statuses, in particular children younger than 10 years of age, in which constipation is less commonly suspected. Further, the Rome-III questionnaires proved to be a feasible and practical diagnostic tool that allowed consistent identification of symptomatic patients.

Based on these findings, we propose that a comprehensive assessment of patients with DMD should include an evaluation for constipation using the QPGS-RIII. This would allow early identification and appropriate management of constipation, thereby improving quality of life and preventing complications.

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