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Chapter 2

Accuracy of diagnostic testing for functional constipation in children: a systematic review

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Submitted
Abstract

Introduction
There is debate which aspects of history and physical examination are most important in discriminating between constipation and no constipation. In case of doubt physicians would like to perform an additional test that can help to establish a firm diagnosis of constipation. Frequently used additional tests in diagnosing childhood constipation are an abdominal radiography, colonic transit time (CTT) and abdominal ultrasonography.

Objective
To perform a systematic literature review evaluating the additional diagnostic value of abdominal radiography, colonic transit time (CTT) and abdominal ultrasonography in the diagnosis of idiopathic constipation in children.

Methods
We systematically searched 2 major electronic databases and reference lists of existing reviews. Eligible studies were those assessing diagnostic accuracy of abdominal radiography, colonic transit time (CTT) or abdominal ultrasonography in children with idiopathic constipation. Data collection had to include a verification of the diagnosis (reference standard). One reviewer rated the methodological quality of the included studies using the QUADAS checklist.

Results
The search identified 767 papers of which 10 diagnostic accuracy studies were included in the final analysis. One systematic review summarized the available diagnostic accuracy studies (n=6) on abdominal radiography up to 2004. The additional 9 studies evaluated diagnostic accuracy of abdominal radiography (n=2), CTT (n=3) and ultrasonography (n=4). We refrained from pooling because of the substantial differences between studies. All studies except one used a case-control study design which will lead to overestimation of test accuracy. Furthermore, none of the studies interpreted the results of the abdominal radiography, ultrasound or CTT without knowledge of the clinical diagnosis constipation. The sensitivity of abdominal radiography, as studied in 6 studies, ranged from 80% (95% CI 65-90) to 60% (95% CI 46-72) and its specificity from 99% (95% CI 95-100) to 43% (95% CI 18-71). Only one study presented sensitivity and specificity of CTT (71% (95% CI 57-83) and (95% CI 82-99), respectively). Two studies presented sensitivity and specificity of ultrasonography. Sensitivity differed significantly between the studies 56% (95% CI 35 – 75) and 100% (95% CI 85-100)). Specificity was 96% (95% CI 77-99) and 89% (95% CI 67-98) respectively.

Conclusion
We found insufficient evidence for a diagnostic association between clinical symptoms of constipation and faecal loading on abdominal radiographs, colonic transit time and rectal diameter on ultrasonography in children. Further well-powered studies of good methodological quality are needed to find the best diagnostic strategy in children suspected of having constipation.
Introduction

Idiopathic constipation is a common problem in children. It is often seen as a minor problem which will either spontaneously resolve or respond to advice on fluid intake and diet. This attitude ignores the impact on wellbeing of the child and family life. In children, constipation and faecal incontinence can lead to social withdrawal, low-self-esteem and even depression. Early diagnosis and treatment may prevent a chronic course with continuation of infrequent painful defecation, psychosocial problems and the need for long-lasting laxative therapy.(1)

History taking and physical examination constitute the most important steps in the diagnosis of idiopathic constipation. However there is debate which aspects of history and physical examination are most important in discriminating between constipation and no constipation. The current best ‘gold standard’ are the ROME III criteria, based on the presence of two or more of a number of well-defined clinical symptoms. However, a diagnosis might be doubtful in case not enough key symptoms of constipation are present or when a rectal examination is not feasible. In such cases one would like to have access to an additional test that can help to establish a firm diagnosis of constipation. Several relatively safe and easily to perform tests are used in daily practice to distinguish between constipation or no constipation.

Under the assumption that faecal retention is one of the main features of constipation, Barr et al (2) introduced a score to appraise faecal retention on a single radiograph of the abdomen. Since then different scoring systems have been developed to assess faecal loading on an abdominal radiograph [29,30]. Based on the same assumption, assessment of stool retention and size of rectum and colon are measured using abdominal ultrasonography. One of the underlying mechanisms of idiopathic constipation is thought to be a disturbance of intestinal motility. Consequently, colonic transit time is assumed to be decreased in children with idiopathic constipation in comparison to healthy children. Based on this assumption transit time is measured using radiopaque markers and abdominal radiography.

We carried out a systematic literature review to evaluate the diagnostic value of abdominal radiography, colonic transit time (CTT) and abdominal ultrasonography in the diagnosis of idiopathic constipation in children.

Methods

Eligible studies were those that assessed the diagnostic accuracy of abdominal radiography, colonic transit time (CTT) or abdominal ultrasonography in children aged 0 to 18 years, with idiopathic constipation suspected on clinical grounds and as defined by the authors. Data collection had to include a (well defined) verification of the diagnosis (reference standard).
Identification of studies
A clinical librarian searched for diagnostic studies published in the Medline and Embase databases from inception to January 2010. Keywords used were: “constipation”, “obstipation”, “faecal incontinence”, “coprostasis”, “encopresis”, and “soiling”. These words were combined with keywords referring to the different types of diagnostic tests that were investigated in the present review. For further relevant studies we searched the reference lists of review articles and the included studies. In case a systematic review was found additional searches started from the date the systematic review stopped searching. We applied no language restrictions. The full search strategy is available from the authors.

Study selection and data extraction
The selection was carried out independently by two reviewers (MYB and MK) on the basis of title and abstract. Specific criteria were used: 1) the study population consisted of children aged 0–18 years or if adults were also included, they had to report separately on children; 2) constipation had to be defined 3) one of the aims of the study was to evaluate the diagnostic value of abdominal radiography, ultrasonography or colonic transit time for functional constipation. All potentially relevant studies, as well as the studies for which the abstracts did not provide sufficient information for inclusion or exclusion, were retrieved as full papers. Systematic reviews using the QUADAS (Quality Assessment of studies of Diagnostic Accuracy included in Systematic reviews)(3) for quality assessment and individual studies were eligible. Excluded were papers concerning children with organic causes of constipation and children with exclusively functional non-retentive faecal incontinence. Two reviewers (MYB and MK) independently assessed eligible studies for inclusion. Disagreement was resolved by discussion. The following characteristics were extracted from each selected study: age range, in- and exclusion criteria, prevalence of constipation in the study population, description of the index test used, description of reference test, data for construction of a two by two table.

Assessment of methodological quality
Study quality of the individual studies was assessed using the QUADAS checklist (3). From the QUADAS checklist we choose six of the best differentiating items (Table 1). Each item is scored as “yes”, “no”, or “unclear”. We did not calculate summary scores because their interpretation is potentially misleading. One reviewer assessed methodological quality (MYB).

Analysis
Wherever possible we calculated sensitivities and specificities with a 95% confidence interval (CI) for each study. In case of clinical heterogeneity (patient population and/or definition of reference and index test are not considered to be sufficiently similar), the results were not pooled.
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Results

The search identified 767 papers of which 23 papers were retrieved for full text review. Of these, 14 studies were excluded as they were no diagnostic accuracy studies (4,5: CTT; 6-11: X-ray), did not include children (12: ultrasound), did not use a control group (13: CTT): did not give a definition of constipation (14: ultrasound; 15: X-ray) or did include children with severe co morbidity (16: CTT). One systematic review did not use QUADAS for quality assessment (17: CTT). (Figure 1)

Of the 10 diagnostic accuracy studies included in the final analysis, 1 systematic review summarized the available diagnostic accuracy studies (n=6) on abdominal radiography up to April 2004(18). The additional 9 studies evaluated diagnostic accuracy of abdominal radiography (n=2)(19,20); CTT (n=3)(20-22) and ultrasonography (n=4)(23-26). Study characteristics of 6 studies reporting data on sensitivity and specificity of radiography are presented in Table 2a and study characteristics of studies on CTT and ultrasonography are presented in table 2b.
Systematic review

In a robust systematic review 6 studies on the diagnostic value of abdominal radiography were included. The included studies were heterogeneous for study design, for the definition of constipation, and the methods used to evaluate the abdominal radiography. In only 4 studies sensitivity and specificity could be calculated (2, 27-29). (Table 3)

Methodological quality

Patients representative of those to receive the test in practice

Only two (19,26) out of the 9 additionally included studies, selected consecutive children with gastrointestinal symptoms related to constipation. All other studies selected cases and controls. In the controls constipation was excluded. (Table 1).
Figure 2: The reported diagnostic association between clinical symptoms and radiographic obstipation. The x- and y-axes present proportions. In case the sensitivity equals 1-specificity the test does not discriminate between constipated and nonconstipated children.

Figure 3: The reported diagnostic association between clinical symptoms and rectal diameter on ultrasonography. The x- and y-axes present proportions. In case the sensitivity equals 1-specificity the test does not discriminate between constipated and nonconstipated children.
Consistency of reference standard

Differential verification bias occurs when the performance of the diagnostic test is verified by a different reference standard. All studies, except three (21, 27, 29) used comparable definitions for constipation including at least weekly frequency of defecation, hard stools.
Accuracy of diagnostic testing for functional constipation in children

Table 2a: Study characteristics of 2 recent studies evaluating abdominal radiography, and of 4 studies included in a previous review, because these 4 studies presented data for calculation of sensitivity and specificity

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>Age range (years)</th>
<th>Index test</th>
<th>Cases (reference standard)</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Çayan 2001 (19)</td>
<td>125</td>
<td>5 to 19</td>
<td>Faecal loading on abdominal radiography according to Blethyn</td>
<td>Less than 3 bowel movements per week for a period of at least 6 months</td>
<td>Children with primary nocturnal enuresis selected at day care centers and schools, without clinical constipation</td>
</tr>
<tr>
<td>Lorijn 2006 (20)</td>
<td>89</td>
<td>Median 9.8 y</td>
<td>Faecal loading on abdominal radiograph according to Leech et al.</td>
<td>At least two of the following: defecation frequency of less than 3 times per week; 2 or more episodes of faecal incontinence per week; production of large amounts of stool once over a period of 7-30 days; the presence of a palpable abdominal or rectal mass (N=52)</td>
<td>Solitary encopresis and/or Soiling without any of the other criteria of constipation Functional abdominal pain (N=37)</td>
</tr>
<tr>
<td>Beckmann 2001 (27)</td>
<td>251</td>
<td>2 to 12</td>
<td>Faecal loading on abdominal radiograph according to Blethyn et al.</td>
<td>Clinical constipation (not further defined)</td>
<td>Children presenting at emergency department with gastrointestinal symptoms</td>
</tr>
<tr>
<td>Leech 1999 (29)</td>
<td>100</td>
<td>1 mo to 14 y</td>
<td>Abdominal radiography divided in 3 segments, each segment given a score from 0 to 5, giving a total score of 0-15.</td>
<td>Children with a clinical diagnosis of constipation (not further specified); N = 33;</td>
<td>Children who underwent IVP for suspected renal tract disorder. N = 67</td>
</tr>
<tr>
<td>Benninga 1995 (28)</td>
<td>101</td>
<td>5 to 14</td>
<td>Abdominal radiography scored according to Barr: Total score: 0-25; score of &gt;10 indicates faecal retention.</td>
<td>At least 2 of the following 4 criteria: Stool frequency &lt;3 times per week; &gt;2 soiling/encopresis episodes per week; periodic passage of very large amounts of stools once every 7-30 d; a palpable abdominal or rectal mass (N = 57).</td>
<td>Symptomatic stool retention based on evidence of &quot;pellet&quot; stools, straining, having a bowel movement no more often than every 3 d, blood streaking on stools, very large stools, history of soiling, positive rectal examination or colonic stool palpation on abdominal examination. Patients with a present history of soiling were excluded; N = 30;</td>
</tr>
<tr>
<td>Barr 1979 (2)</td>
<td>42</td>
<td>3 to 7</td>
<td>Abdominal radiography scored according to Barr: Total score: 0-25; a score of &gt;10 indicated symptomatic stool retention.</td>
<td>Solitary encopresis and/or Soiling without any of the other criteria of constipation (N = 30). Recurrent abdominal pain Severe enough to interfere with day-to-day activities over at least a 3-mo period without any of the other symptoms of PC (N = 14).</td>
<td>Patients with a present history of soiling were excluded; N = 30;</td>
</tr>
</tbody>
</table>

and difficulty in evacuating. Gutiérrez (21), Beckmann (27) and Leech(29) did not specify their diagnosis of constipation. (Table 1)
None of the studies interpreted the results of X-ray, ultrasound or CTT without knowledge of the clinical diagnosis constipation. (Table 1)

Explanation of withdrawals

In most studies the selection procedure was not clearly described. Only three studies (21,23,24) described the reason and number of children that did not underwent the diagnostic test. (Table 1)
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Data synthesis and analysis

Were possible we calculated sensitivity and specificity. (Table 3).

Abdominal radiography. We identified 1 systematic review, 4 included studies reported data that enabled calculation of sensitivity and specificity, in addition we found 2 more recent studies. All studies except one (19) were performed in referred children. In the systematic review conflicting evidence was found for a diagnostic association between clinical symptoms of constipation and faecal loading in abdominal radiographs in children. Çayan et al (19) studied children with primary nocturnal enuresis in an open population. They scored faecal loading on abdominal plain film according to the method of Blethyn et al (30).
Table 3: Diagnostic value of abdominal radiography, ultrasonography and CTT in diagnosing clinical constipation

<table>
<thead>
<tr>
<th>Source</th>
<th>Number of patients with clinical constipation / number of patients without clinical constipation</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beckmann 2001 (27)</td>
<td>180/71</td>
<td>61 (53-68)</td>
<td>55 (43-67)</td>
</tr>
<tr>
<td>Leech 1999 (29)</td>
<td>33/67</td>
<td>76 (58-89)</td>
<td>75 (63-85)</td>
</tr>
<tr>
<td>Benninga 1995 (28)</td>
<td>57/44</td>
<td>60 (46-72)</td>
<td>43 (18-71)</td>
</tr>
<tr>
<td>Barr 1979 (2)</td>
<td>30/12</td>
<td>80 (65-90)</td>
<td>90 (74-98)</td>
</tr>
<tr>
<td>De Lorijn 2006 (20)</td>
<td>52/37</td>
<td>75 (61-86)</td>
<td>59 (42-75)</td>
</tr>
<tr>
<td>Çayan 2001 (19)</td>
<td>10/115</td>
<td>70 (35-93)</td>
<td>99 (95-100)</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klijn 1986 (23)</td>
<td>23/26</td>
<td>100 (85-100)</td>
<td>89 (70-98)</td>
</tr>
<tr>
<td>Joensson 1997 (24)</td>
<td>27/22</td>
<td>56 (35-75)</td>
<td>96 (77-99)</td>
</tr>
<tr>
<td>CTT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Lorijn 2006 (20)</td>
<td>52/37</td>
<td>71 (57-83)</td>
<td>95 (82-99)</td>
</tr>
</tbody>
</table>

Cut-off values that defined constipation were not presented. De Lorijn et al (20) used the Leech method (30) to score abdominal radiography. As optimal cut-off score they found a score of 9, out of a maximum of 15; where all scores above 9 indicated constipation. In an ROC analysis they found an AUC of 0.68 (95% CI 0.58 to 0.80) indicating poor diagnostic accuracy.

Colonic transit time. De Lorijn et al. (20) used the method of Bouchoucha et al. (31) to determine the CTT. The radiography on day 7 was used to count the number of markers visible in the colon. The optimal CTT to define constipation was found to be 54 hours, leading to a sensitivity of 79% and a specificity of 92%. The most frequently used cut-off value for CTT in the literature is 62h, leading to a sensitivity of 71 % and a specificity of 95% (table 3). The AUC for CTT was 0.90 (95% CI 0.83 to 0.96) indicating good diagnostic accuracy. Gutiérrez et al. (21) used the method of Bouchoucha et al. (31) to establish CTT. The radiography on day 7 was used to count the number of markers visible in the colon. A cut-off value that defined constipation was not presented. In constipated children the mean CTT was significantly prolonged compared to the control group (49,57 ± 25,38 (mean ± SD) compared to 29,08 ± 8,3). Not surprisingly, CTT was inversely related to the number of defecations per week. Zaslavsky et al. (22) used the method as described by Metcalf et al. (32). The radiography on day 4 was used to count the number of markers visible in the colon. No cut-off values to define constipation were presented. In constipated children the mean CTT was significantly different from that in the control group (58,25 ± 17,46 compared to 30,18 ± 13,15).
Ultrasonography. Klijn et al. (24) studied children with lower urinary tract dysfunction. They measured the diameter of the rectum behind the bladder in children with a full bladder. There was a statistically significant difference in the diameter of the rectum between the constipated group and the control group. Mean diameter in the constipated vs control group 4.9 vs 2.1 cm. A cut-off value of 3.3 cm, where >3.3cm indicated constipation, lead to a sensitivity of 100% (95% CI (85-100)) and a specificity of 89% (95% CI (70-98)). Joensson et al. (23) measured rectal diameter in the transverse plane, using the method as described by Klijn et al. (24). All children had a partly full bladder. In all included children it was possible to visualize the transverse diameter of the rectum at least 3 hours after the last bowel movement. Constipated children had a significantly larger rectal diameter than healthy children (39.6 ± 8.2mm vs 21.4 ± 6.0mm). Using a cut-off value for constipation of 33.4 mm 13 children would be misclassified. After laxative treatment the rectal diameter of the constipated children reduced significantly to 26.9 ±5.6 mm. Behind the urinary bladder, Singh et al. (25) measured the rectal crescent in cm. The bladder of the children had to be partially full. The median rectal crescent size in children with constipation was 3.4 cm (range 2.10 to 7.0; IQR 35.3) as compared with 2.4 cm (range 1.3 to 4.2; IQR 0.72) in healthy controls. A receiver operating characteristics analysis found an AUC of 0.847 (95% CI 0.79 to 0.904) indicating good diagnostic accuracy. Cut-off values for constipation were not presented. Bijos et al. (26) calculated a recto pelvic ratio by dividing the transverse diameter of the rectal ampulla by the transverse diameter of the pelvis. In children with functional constipation the mean recto pelvic ratio was 0.22 ± 0.05 compared to healthy controls 0.15 ± 0.04. The difference was statistically significant in all age groups.

Discussion

In this systematic review of studies on the diagnostic value of additional tests for childhood constipation, we could include one systematic review of 6 studies on abdominal radiography, 2 additional studies on abdominal radiography, 3 studies on CTT and 4 on rectal diameter at ultrasonography. All, but two of the individual studies had a case control design. Studies that recruited a group of healthy controls or controls in which other gastrointestinal complaints like abdominal pain were excluded are likely to overestimate diagnostic accuracy. Therefore the results of this review will give an overestimation of the true diagnostic accuracy of the tests evaluated. Most studies had small sample sizes. This may result in large 95% CI. Pooling of data would have been a solution to overcome the problem of small sample size, nevertheless, we refrained from pooling because of the substantial differences between studies. Although there was wide heterogeneity between the studies, all studies were homogeneous in their hospital based setting. Therefore, the results of our review cannot be generalized to general practice.
Reference standard

Constipation can be diagnosed by a detailed medical history and a thorough physical examination including a digital rectal examination. Constipation is a syndrome characterized by typical symptoms. The included studies used different definitions for constipation. Thereafter the reference standard varied between studies. This hampered comparison of the results. Recently a committee of clinical experts proposed to use a uniform definition for constipation, the so-called ROME III criteria. The validity of the ROME III criteria has not been tested, partly because of the lack of an objective reference standard. In primary care the ROME criteria are thought to be too restrictive. A diagnosis of constipation might be considered in case not enough key symptoms of constipation are present or when a rectal examination is infeasible. None of the included studies evaluated the diagnostic value of the tests in a population were additional information on diagnosis would be helpful.

Abdominal radiography

The conclusion of the authors of the systematic review was that there is conflicting evidence for a diagnostic association between clinical symptoms of constipation and faecal loading in abdominal radiographs in children. The two additional studies included in this review add to the evidence for no association. Based on this evidence, the recently published NICE guideline concluded that abdominal radiography should not be recommended as an additional test for constipation in children (33). Although the conclusion of the NICE guideline seems justified one should keep in mind that none of the included studies evaluated abdominal radiography in a population in which constipation is suspected but criteria for constipation are not sufficiently fulfilled. In contrast even in case-control studies were accuracy will be grossly overestimated, the diagnostic value of abdominal radiography was low.

Colonic Transit Time

Only one study presented sensitivity and specificity of CTT (71% (95% CI 57-83) and (95% (95% CI 82-99), respectively). The AUC in this study was 0.90 (95% CI 0.83-0.96), indicating good discrimination between constipated and non-constipated children. Compared to abdominal radiography the accuracy of CTT was significantly better in this study population (AUC 0.68 (95% CI 0.58-0.80). (20). These results will be an overestimation of the diagnostic value of CTT. Cases and controls did not represent a clinically relevant population. A one-year follow-up study of children treated with laxatives or biofeedback, however, showed results in favour of the discriminative ability of CTT (34). In this study children with a total CTT of > 100 hours had less treatment successes after 12 months then children with a shorter total CTT. Before recommending CTT as a diagnostic test for constipation, however, further studies in clinically relevant populations are needed.
Ultrasonography

Pelvic ultrasound can show the impression of the rectum behind the urinary bladder. It is easy to measure the transverse rectal diameter. Ultrasonography is not invasive, does not involve radiation and might therefore be a potentially feasible test in primary and secondary care. Measuring rectal diameter was associated with the results of digital rectal examination and therewith seems to assess faecal impaction. Recently it was reported that 85% of primary care physicians did not perform digital rectal examination before referral for constipation (35). It is suggested that ultrasonography might replace digital rectal examination because it will be less unpleasant. Our results show that as for now, there is insufficient evidence that the transverse diameter can be used as a predictor of constipation and faecal impaction.

Future studies

Future studies should be performed in clinically relevant populations of children suspected for constipation. One might argue that a clinical diagnosis of constipation is a substitute of an adequate reference standard for constipation in children. In case an adequate reference standard is lacking, follow-up studies (preferably randomised) are needed to quantify the effect of a diagnostic test on patient outcome. Evaluating a test on patient outcome involves the evaluation of the diagnostic tests (clinical diagnosis, and abdominal radiography, ultrasonography or colonic transit time) plus current administered therapies (laxatives) combined (36). In addition not only the accuracy of the test should be evaluated but also the additional diagnostic value above clinical characteristics should be addressed.

Conclusion

We found insufficient evidence for a diagnostic association between clinical symptoms of constipation and faecal loading on abdominal radiographs, colonic transit time and rectal diameter on ultrasonography in children. Further well-powered research of good methodological quality is still needed to find the best diagnostic strategy in children suspected of having constipation.
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