World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i11.1468

World J Gastroenterol 2011 March 21; 17(11): 1468-1474
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Factor analysis identifies subgroups of constipation

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Supported by National Health and Medical Research Council Australia (ID 455213)
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Received: June 16, 2010 Revised: January 13, 2011
Accepted: January 20, 2011
Published online: March 21, 2011

Abstract

AIM: To determine whether distinct symptom groupings exist in a constipated population and whether such grouping might correlate with quantifiable pathophysiological measures of colonic dysfunction.

METHODS: One hundred and ninety-one patients presenting to a Gastroenterology clinic with constipation and 32 constipated patients responding to a newspaper advertisement completed a 53-item, wide-ranging self-report questionnaire. One hundred of these patients had colonic transit measured scintigraphically. Factor analysis determined whether constipation-related symptoms grouped into distinct aspects of symptomatology. Cluster analysis was used to determine whether individual patients naturally group into distinct subtypes.

RESULTS: Cluster analysis yielded a 4 cluster solution with the presence or absence of pain and laxative unresponsiveness providing the main descriptors. Amongst all clusters there was a considerable proportion of patients with demonstrable delayed colon transit, irritable bowel syndrome positive criteria and regular stool frequency. The majority of patients with these characteristics also reported regular laxative use.

CONCLUSION: Factor analysis identified four constipation subgroups, based on severity and laxative unresponsiveness, in a constipated population. However, clear stratification into clinically identifiable groups remains imprecise.

Key words: Factor analysis; Constipation; Symptoms; Clusters; Laxatives

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Dinning PG, Jones M, Hunt L, Fuentealba SE, Kalanter J, King DW, Lubowski DZ, Talley NJ, Cook IJ. Factor analysis identifies subgroups of constipation. *World J Gastroenterol* 2011; 17(11): 1468-1474 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i11/1468.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i11.1468

INTRODUCTION

Constipation is a heterogeneous disorder, the most consistent generic descriptor for which is difficult or infrequent passage of stool[1,2]. A fundamental aim in researching and treating any heterogeneous disorder is to subclassify

the condition into categories that are predictive of either pathophysiology or treatment outcome. Constipation is currently conceptualized in three broad categories: normal transit constipation (NTC), slow transit constipation (STC) and disorders of defecation or rectal evacuation[3-5]. This distinction among subgroups, in some cases, has proven beneficial in planning treatment and in predicting therapeutic outcome[4,6-12].

It remains unknown whether subtypes of constipation can be identified reliably on the basis of symptoms. The mathematical techniques of factor and/or cluster analysis, to determine whether certain symptoms and/or subjects do group together more than expected by chance, can provide empiric evidence of the existence of true syndromes. Studies applying these techniques have found conflicting results, with Mertz *et al*[13] identifying 3 subtypes while Eltringham *et al*[14] did not. These findings suggest that the *a priori* assumption that these subtypes are distinct or distinguishable from each other on the basis of symptoms may be incorrect, or that investigators have yet to combine the correct symptoms to identify pathophysiologically distinct abnormalities.

Utilizing a 53-item specific constipation questionnaire and colonic scintigraphy our aim was to identify symptoms or groups of symptoms that identify underlying severe constipation subgroups. Specifically, we hypothesized that within this constipation population at least three distinct subgroups, STC, evacuation disorder and irritable bowel syndrome (IBS), can be identified by groups of symptoms and that these symptom groups will be predictive of specific underlying objective physiological measures such as colonic transit time.

MATERIALS AND METHODS

Design of the questionnaire and assessment of symptoms

The Sydney Constipation Questionnaire (SCQ) was derived from the previously validated Bowel Disease Questionnaire[15] and the Bowel Symptom Questionnaire[16]. The SCQ comprises 53 items, including 42 symptom items and the validated Bristol stool scale[17]. Additional constipation items were then added and the face validity was assessed by responses from 29 internationally recognised constipation experts who were asked to rate each question according to clinical relevance. The test-retest reliability of the final questionnaire was evaluated in 47 patients who repeated the questionnaire within 3 wk of initial testing[18]. The design of the questionnaire took place long before the release of Rome Ⅲ criteria for bowel[19] and anorectal[20] dysfunction, nevertheless the questionnaire does contain all of the symptomatic questions that define constipation, IBS and outlet obstruction by the Rome Ⅲ criteria.

Population sample

Subjects were obtained through two sources: (1) *via* referrals from specialists in the Sydney area; and (2) by direct advertisement that specified criteria approximating tertiary-referred subjects. The impact of subject source was considered in the statistical analysis. Overall, the sample was designed to reflect community members suffering serious constipation symptoms. Subjects were deliberately not selected based on Rome Ⅲ constipation criteria, but rather on the basis of serious symptoms to avoid making assumptions and because we wanted also to examine the proportion of the study cohort and its clusters that would be positive for Rome Ⅲ criteria for constipation or IBS.

Referrals to colorectal surgeons or gastroenterologists in Sydney metropolitan region, seeking treatment for constipation, were recruited over a 4-year period and were given a questionnaire if they fulfilled the following criteria: (1) had not undergone any form of colectomy, rectocele or rectal prolapse repair; and (2) their constipation was not deemed secondary to a metabolic or neurological disease or pregnancy. Additionally, the questionnaire was given to potential patients who responded to advertisements in Sydney newspapers recruiting subjects for a randomized control trial of sacral nerve stimulation for the treatment of constipation (in progress; to be reported in future). These potential patients were screened during an initial phone conversation and if they fulfilled the criteria listed above the questionnaires were mailed out to them. As these were chronically constipated patients, who for the most part had been taking laxatives for many years, they were not asked to report on what their symptoms are, were or might be, in the absence of laxatives. Studies have shown that the correlation between a patient's reported stool frequency and actual measures is poor[21] and in our experience a patient's ability to recall symptoms from the years prior to laxative use is also poor.

Allowing 3 wk for the questionnaire to be completed and returned, each non-responder was then phoned and asked if they intended to return the questionnaire. A proportion of community responders had decided that their symptoms were not severe enough to warrant sacral nerve stimulation and these patients did not return the questionnaire. Allowing an additional 4 wk, all other non-responders were excluded from the study. All participants in this study gave written, informed consent and the study was approved by the Human Ethics Committees of the South Eastern Area Health Service, Sydney and the University of New South Wales.

A priori symptom groups

Three symptom groups were defined *a priori*: (1) STC was considered to comprise infrequent bowel movements (less than 2 defecations/wk), lack of defecation urge, excessive straining and hard stools[22-24]; (2) Obstructed defecation was classified when all of the following symptoms were present: (a) an inability to initiate defecation following the urge to do so, or difficulty with stool evacuation; (b) excessive straining at stool more than 25% of the time or self-digitation to facilitate defecation more than 25% of the time; and (c) a feeling of incomplete evacuation after

defecation[1,22,25-29]; and (3) IBS classified those patients with symptoms of abdominal pain and bloating that improve with defecation or in whom the onset of such symptoms is associated with a change in frequency or form of the stool[19,22,24,30].

Transit studies

Colonic transit was measured using a standard nuclear medicine technique[31,32]. Briefly, the subjects attended a Nuclear Medicine Department on a Monday morning and were given 4 MBq ^{111}In-DTPA orally at approximately 9:00 am. They returned to the department the same day at approximately 3:00 pm and on subsequent days at approximately 24, 48, 72 and 96 h following the oral administration. On each occasion, anterior and posterior abdominal images were obtained each for 10 min using a large field-of-view gamma camera and medium energy collimator. Background images were obtained for background correction. All laxative medications were stopped 3 d before and during the scan. No effort was made to control the patient's diet during the scan period. Method of the scintigraphic analysis is reported elsewhere[33]. Briefly, at each time point, profiles of the activity along the colon were derived from a geometric mean image obtained from the anterior and posterior images. Total percent retention (T%R) and mean activity position (MAP) at each time were calculated for each subject. T%R indicates the retained activity in the colon using the value at 6 h as 100%. MAP indicates the geometric center of the activity, where position 0 is at the cecum, position 98 at the anus, and position 99 being excreted activity. The scintigraphic definition of delayed transit constipation was met if the study showed isotope retention of greater than 9% in the right (cecum to mid-transverse) or left colon (mid-transverse to distal descending colon) at 72 h[31,32].

Data analysis

Since this has been a vexed question to date, a naturalistic approach was adopted in which multivariate statistical techniques were used to identify distinct clusters of individuals with respect to bowel symptom patterns and these clusters were then examined with respect to their symptom profiles to determine what, if any, clinically meaningful differences existed between them. Analysis proceeded in two steps; the first reduced the data dimensionality from 42 observed symptom variables to 15 latent variables which were then used in the second step in a cluster analysis to form internally homogeneous clusters of individuals: details follow. The first step identified independent dimensions of symptom profile through principle components analysis followed by orthogonal rotation of the factor space. Identifying independent dimensions of bowel symptoms has several advantages. Bowel symptom questionnaires typically ask several questions around a given bowel symptom to fully characterize patients' symptomatology. Despite the clinical value of these questions, they are typically strongly correlated, leading to statistical redundancy amongst them. In addition, cluster analysis is prone to dominance by scales that are numerically large and factor scores calculated for individuals follow a unit of normal distribution (mean zero, standard deviation 1.0) and are therefore standardized. Factors were interpreted and used in the subsequent cluster analysis if the corresponding eigenvalue was > 1.0, which corresponds to approximately 2% explained variance in the original data. The variance in the original data explained by each factor is reported in Table 1, as well as the total explained variance across all 15 factors used. A score was calculated for each factor for each subject, which is in effect a weighted sum across all original data items deemed to load on a given factor. These are reported in Table 1, along with the rotated factor loading for each item, using a criterion of rotated factor loadings > 0.4 (in absolute value). Factor loadings can be interpreted as the correlation between a given original data item and its corresponding latent variable. In the second analytic step, these scores were used in a non-hierarchical (K-Means) cluster analysis. It is important to note that only symptom latent variables were utilized in cluster formation, not transit times. Based on an *a priori* expectation of a moderate number of distinct clusters, solutions between 1 and 6 clusters were considered. A single cluster solution would imply the subjects were not differentiated in any systematic fashion, while six clusters would represent a quite complex system of constipation subgroups. The choice of cluster solution adopted was a trade-off of within-cluster homogeneity and minimizing unnecessary complexity. In a K-Means analysis the algorithm assigns individuals to clusters such that the overall within-cluster variance is minimized and the between-cluster variance is maximized, given the prespecified number of clusters. Euclidean distance was used to measure the distance between individual points and their cluster centroid.

Determination of the clinical value of the clusters identified was through a comparison of profiles of individual symptom items and by comparing rates of *a priori* criteria, Rome Ⅲ-defined constipation, IBS and outlet dysfunction, and rates of slow transit measured as described earlier.

RESULTS

The questionnaire was given to a total of 326 individuals suffering from constipation. Of these, 246 were referrals to colorectal surgeons or gastroenterologists and 80 were recruited from the community by advertisements. Of these, a total of 223 responded, representing an overall response rate of 68% [191 (78%) response rate for clinic cases; 32 (40%) response rate for community cases]. Of the 223 returned questionnaires, 4 were not able to be utilized (2 incomplete; 2 were multivariate outliers) leaving n = 217 for final analysis. There was no significant age or gender difference between the clinic group (45 ± 17 years; range 18-81 years; 13 M:178 F) and community groups (56 ± 20 years; range 24-82 years; 5 M:27 F). The

Table 1 Factor loadings derived from the rotated factor matrix

	Factor loading	Percent variance
Factor 1: Straining		17.3
Strain hard: How often	0.82	
Straining: How bad usually	0.80	
Straining: How long	0.76	
Straining: How often	0.71	
How long to bowel motions take	0.59	
How often incomplete evacuation	0.55	
How often unsuccessful attempts	0.52	
Frequency of any bowel problems	0.47	
How troubling is constipation	0.41	
Change positions: How often	0.35	
Factor 2: Pain frequency and severity		8.4
Abdominal pain: How often	0.80	
Pain in belly: Past 3 mo	0.79	
Abdominal pain: Severity	0.79	
Abdominal pain: Length	0.65	
Rectal mucus: How often	0.41	
Rectal pain: How often	0.39	
Pain in belly: Past 12 mo	-0.58	
Factor 3: Duration of constipation		6.5
Constipation: How many years	0.89	
Straining: How many years	0.87	
Abdominal pain: First occurrence	0.57	
Factor 4: Irritable bowel syndrome symptoms		5.6
Abdominal pain: Improved after bowel motion	0.75	
Abdominal pain: Improved after passing gas	0.70	
Experience lower abdominal pain	0.63	
Bowel motions: Harder than usual past 12 mo	0.40	
Factor 5: Urge frequency		4.1
Urge for bowel motion: How often	0.72	
Perceive an urge before attempt to open bowels	0.68	
Visits to toilet: How often	0.56	
Urgency for bowel motion: How often	0.42	
Factor 6: Diarrhea frequency		3.8
Loose/watery stool: How often	0.75	
Pebble-like stool: How often	-0.42	
Rectal disimpaction: How often required	-0.45	
Hard/lumpy stool: How often	-0.63	
Factor 7: Alternating between diarrhea and constipation		3.4
Usually alternating	0.87	
Usually constipated	-0.86	
Factor 8: Bloating frequency		3.2
Stomach swelling in the last 12 mo: How often	0.71	
Felt bloated in the last 12 mo: How often	0.68	
Felt blocked: How often	0.47	
Factor 9: Laxative efficacy		2.9
Laxative use: Longest gap between taking and bowel motion	0.70	
Bowel motions: Fewer than usual past 12 mo	0.56	
Laxative use: How often	0.44	
Factor 10: Rectal urgency		2.7
Urge from rectum	0.89	
Urge from abdomen and rectum	-0.80	
Factor 11: Bowel motion frequency		2.6
Longest gap between bowel motions	0.81	
Usual bowel frequency	-0.56	
Factor 12: Change in bowel frequency		2.4
Bowel motions: More than usual past 12 mo	0.74	
Bowel motions: Looser than usual past 12 mo	0.62	
Factor 13: Abdominal urge		2.3
Experience an urge from abdomen	0.89	
Factor 14: Diarrhea predominance		2.2
Usually experience diarrhea	0.79	
Factor 15: Antecedent to constipation		2.0
An antecedent for the constipation	0.71	
Experience upper abdominal pain	0.51	
Total (1-15)		69.3

mean age of the entire group was 47 ± 17 years (range 18-82 years).

Colonic transit was performed in all patients who had access to a nuclear medicine facility; in total 100 patients (52%) underwent the procedure study.

Factor analysis

The factor analysis produced a rotated factor matrix comprising 15 factors. Table 1 lists these 15 factors and the labels that we have attached to each factor, along with the loadings of the associated questions. For brevity, we have only shown questions within each factor for which the absolute value of the loading was ⩾ 0.35. While this process is simply an intermediary step towards cluster analysis, there are a number of potentially relevant observations to be made from this matrix. An IBS-like factor emerged, indicating that IBS-like symptoms stand out as a distinct entity in this population. Despite the population being selected for its constipation, a diarrhea factor emerged, probably accounted for by laxative usage (see below).

Cluster analysis

Cluster 1: Patients in this cluster are less likely than average to report preservation of their defecatory urge (compared to cluster 4) despite 80% using laxatives regularly. This cluster is relatively laxative-responsive with 83% describing laxatives as somewhat or very effective. Although clusters 1 and 4 share some similarities, they differ dramatically in their responsiveness to laxatives. Cluster 1 patients experience less upper abdominal pain than patients in clusters 2 and 4. Patients in cluster 1 have more IBS-like features than those in other clusters and they gain pain relief following a bowel action.

Cluster 2: This group has features similar to those of cluster 1 but when compared with cluster 1, their pain is somewhat less severe and less prevalent and they describe a shift in the site of their pain from lower to the upper abdomen. They describe similar laxative usage and responsiveness to patients in clusters 1 and 3. These patients are least likely to visit the toilet daily (63%) despite the fact that they report the highest rate of "urge prior to attempting to defecate" (72%). They are relatively laxative-responsive with 76% reporting them "somewhat or very effective".

Cluster 3: Patients in this cluster have the lowest pain scores of all 4 clusters, have a short history of constipation and are more likely to report a weekly stool frequency within the Rome Ⅲ defined range for constipation. They report the lowest laxative usage, but they are the most laxative-responsive of all patients. They rarely report a feeling of rectal blockage and are less likely to adopt self digitation to facilitate evacuation. These patients never report diarrhea and rarely report hard stool.

Cluster 4: These patients report the highest pain scores and are strikingly unresponsive to laxatives, despite re-

Table 2 Summary of the proportion of patients within each cluster who were positive for constipation[1] or irritable bowel syndrome on the basis of Rome Ⅲ criteria, as well as proportions in each group with slow transit constipation

	Clusters (4-fold solution)			
	1 (n = 71)	2 (n = 44)	3 (n = 34)	4 (n = 43)
Rome Ⅲ constipation				
Yes	84.50%	77.30%	58.80%	72.10%
Rome Ⅲ IBS				
Yes	52.10%	27.30%	20.60%	53.50%
Outlet dysfunction				
Yes	52.10%	56.80%	52.90%	48.80%
Colonic transit	n = 43	n = 28	n = 16	n = 29
Delayed transit	74.40%	71.40%	62.50%	79.30%
Normal transit	25.60%	28.60%	37.50%	20.70%

[1]With the exception that symptoms were assessed irrespective of laxative usage. IBS: Irritable bowel syndrome.

porting the highest laxative usage of all (98% use them > 50% of the time). Abdominal pain is described as more severe, more frequent and lasting longer than in the other clusters. Importantly, patients in this cluster report that a bowel motion does not relieve their pain. They are less likely to have an antecedent (e.g. hysterectomy, pregnancy) than those in the other clusters. In comparison with other clusters, these patients report increased frequency of defecatory urge with 30% reporting an urge to defecate more than 3 times/d, more frequent toilet visits (60% > once/d), frequent unsuccessful attempts at defecation (73%) and frequent sense of blockage (66%) during passage of stool.

Correlation with Rome Ⅲ criteria for constipation or IBS

In this population with severe constipation, the positivity rate for Rome Ⅲ constipation was 59%-85% across the 4 clusters (Table 2). In this severely constipated population, with the exception of cluster 3, 78%-98% were habitual laxative users. Clusters 1 and 4 are characterized by high rates of Rome Ⅲ IBS (over 50%, Table 2) compared with 20%-27% in clusters 2 and 3 (Table 2). The majority (92%) of patients that met Rome Ⅲ IBS criteria were also associated with heavy laxative use.

Correlation with symptomatically-defined obstructed defecation

A remarkably constant 49%-57% of patients reported symptoms that have traditionally been attributed to obstructed defecation. The prevalence of this pattern did not differ among the four clusters.

Correlation with scintigraphically confirmed slow transit

Between 63% and 79% of patients had slow transit (Table 2). The prevalence of slow transit was least in cluster 3 (63%), the cluster with the mildest symptoms, but this still represents a sizable majority of this group. Of the 25% of severely constipated patients that report > 3 bowel motions a day, 75% have demonstrable STC. The vast majority of these patients are also heavy laxative users, report mainly liquid stool, and a feeling of incomplete evacuation.

DISCUSSION

The ability to subtype severely constipated patients based upon symptoms has merit because it focuses and systematizes epidemiological enquiry, and has the potential to dictate logical and cost effective investigation algorithms for clinicians, to influence management and to predict therapeutic outcome. However, this study highlights the difficulties in using symptoms as discriminators of severe constipation subtypes. Although four groupings were identified by cluster analysis, it is difficult to attach clearly recognizable pathophysiological labels to these clusters. The major finding of this study is the identification of a group (cluster 4) with long history of constipation, a profound lack of response to laxatives despite extremely high laxative usage, and the highest pain scores. In contrast, cluster 3 was characterized by low pain scores, low rates of co-morbidity and the lowest rate of delayed colonic transit. Overall, our data appear to suggest subtypes based on severity and chronicity of disease which is reflected in rates of, and responsiveness to, laxative therapy.

The positivity rate for Rome Ⅲ-defined constipation was 59%-85% across the four clusters. Interestingly, of the patients that did not meet the Rome criteria, 63%-80% across the 4 clusters have demonstrable delayed colonic transit. In other words, Rome Ⅲ criteria will not pick up a substantial proportion of people who are severely troubled by constipation and who clearly have markedly disturbed physiology as confirmed by delayed colonic transit. In addition, a large proportion of patients, particularly in clusters 1 (52%) and 4 (54%), met the Rome Ⅲ criteria for IBS. In our experience this overall high prevalence of criteria satisfying the definition of IBS is in keeping with the situation commonly encountered by clinicians and has been reported previously[34].

One of the potential problems with subtyping constipated patients into categories based on questionnaire data is the prevalence of laxative use. Given that the approach to constipation subtyping used in this study relied upon symptom patterns, laxative use is a potential confounder because these agents can induce symptoms of bloating and pain and alter stool frequency/consistency. While laxative use is mentioned in previous studies[13,14,34-36], little or no attempt is made to discern their impact upon symptoms. For example, of those patients that met IBS criteria in this study, 92% were heavy laxative users. Asking patients to detail their symptoms in the absence of laxatives has been attempted[14]. However, in our experience such questions are difficult to answer for a chronically constipated population who, for the most part, have been taking laxatives for many years. Indeed, previous studies have shown a poor concordance between a patient's recollection of events and actual measures[21].

Furthermore, high rates of laxative use may also con-

found attempts to identify symptom-based distinct subtypes of constipation that correspond to pathophysiological subtypes. This becomes evident when examining the correlation between delayed transit and infrequent stool frequency. There is literature to support infrequent bowel movements in predicting delayed transit[36-38]. Those studies found that < 3 bm/wk predicted delayed transit in 85%-100% of patients. Indeed, it is the practice of some groups to only evaluate transit formally in patients with infrequent stools[39]. However, this study indicates that a high percentage (75%) of patients who use their bowel > 3/d have demonstrable slow colonic transit. Importantly, these patients also report high laxative use. Therefore, these data suggest that normal stool frequency, in the context of concurrent laxative use, certainly does not preclude STC.

Delayed colonic transit was found in the majority of patients in whom scintigraphy was performed, which is comparable with the reports of others[38,40,41]. While it was lowest in cluster 3, a sizable 63% in this relatively mildly affected group had delayed transit; hence, our findings suggest that delayed transit cannot be predicted accurately on the basis of a combination of symptoms.

Using existing criteria for obstructed defecation based purely on symptoms[1,22,25-28], this syndrome was both common and equiprevalent across all four clusters (49%-57%). This lack of discriminatory ability of clusters to co-localize with these symptoms supports the consistent findings of a number of investigators that symptoms are not predictive of pelvic dyssynergia demonstrated by anorectal manometry and balloon expulsion testing[34-36,42] or demonstrated by defecography[43]. Grotz *et al*[34] found that only a sense of anal blockage correlated with proven pelvic floor dysfunction. However, as Grotz *et al*[34] point out, the usefulness of this finding must be questioned because this symptom was present in 67% of pelvic floor dysfunction but was found in 50% of patients with STC and in 53% with NTC. Indeed, in their multivariate analysis, they could not identify any colonic symptoms as discriminators of constipation subtypes.

Clinical history remains a "blunt instrument" and while combinations of symptoms do point towards 4 subsets of constipation, we are some distance yet from defining those subsets in unequivocal and specific terms. In light of the overlap with IBS symptoms in this study, it behooves the clinician to consider severe delayed transit in patients presenting with constipation-predominant IBS as this may influence management and avoid mislabeling the patient. Currently, combinations of symptoms cannot predict accurately whether the patient that is categorized into one of these 4 clusters has normal or delayed transit. However, laxative use in severely constipated patients may influence the reported symptoms and this potential confounder needs to be taken into consideration when interpreting these results.

COMMENTS

Background

Constipation is often perceived as a benign, easily treated condition; however, a number of studies confirm that constipation has a significant adverse effect on a patient's quality of life. Constipation is a heterogeneous disorder and a fundamental aim in researching and treating any heterogeneous disorder is to subclassify the condition into categories that will help guide treatment options. As a patient's symptoms are the first point of discussion with their doctor, the ability to subclassify on the basis of symptoms is a primary goal.

Research frontiers

The mathematical techniques of factor and/or cluster analysis have been used in an attempt to determine whether certain symptoms can predict constipation subtypes. However, studies applying these techniques have found conflicting results suggesting that the *a priori* assumption that these subtypes are distinct or distinguishable from each other on the basis of symptoms may be incorrect, or that investigators have yet to combine the correct symptoms to identify pathophysiologically distinct abnormalities. Utilizing a 53-item specific constipation questionnaire our aim was to identify groups of symptoms that identify underlying severe constipation subgroups, such as slow transit constipation, evacuation disorder and irritable bowel syndrome.

Innovations and breakthroughs

Factor analysis of 221 questionnaires yielded a 4 cluster solution with the presence or absence of pain and laxative unresponsiveness providing the main descriptors. Amongst all clusters there was a considerable proportion of patients with demonstrable delayed colon transit, irritable bowel syndrome positive criteria and regular stool frequency. Therefore, as with previous studies, we have demonstrated that significant overlap exists between mathematically defined clusters of symptoms and globally accepted sub-types of constipation.

Applications

Laxative use in severely constipated patients may influence the reported symptoms and this potential confounder needs to be taken into consideration when interpreting these results.

Peer review

This is an important study in which authors attempted to evaluate whether cluster of symptoms can help to understand pathophysiology of constipation.

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