TITLE PAGE

Title: Cyclic Vomiting Syndrome is a Prevalent and Under-recognized Condition in the Gastroenterology Outpatient Clinic.

Short running page heading: Prevalence of Cyclic vomiting syndrome.

Authors: Rebecca C. Sagar[1,2], Ruchit Sood[1,2], David J. Gracie[1,2], Matthew J. Gold[3], Natalie To[1,2], Graham R. Law[4], Alexander C. Ford[1,2].

[1]Leeds Gastroenterology Institute, St James's University Hospital, Leeds, UK

[2]Leeds Institute of Biomedical and Clinical Sciences, University of Leeds, Leeds, UK.

[3]School of Medicine, University of Leeds, Leeds, UK.

[4]School of Health and Social Care, University of Lincoln, Lincoln, UK.

Abbreviations:

BMI	body mass index
CVS	cyclic vomiting syndrome
FGID	functional gastrointestinal disorder
GI	gastrointestinal
IBS	irritable bowel syndrome
HADS	hospital anxiety and depression scale
PHQ-15	patient health questionnaire-15
SD	standard deviation

Correspondence: Professor Alexander C. Ford

Leeds Gastroenterology Institute

Room 125

4th Floor

Bexley Wing

St James's University Hospital

Beckett Street

Leeds

United Kingdom

LS9 7TF

Email: alexf12399@yahoo.com

Telephone: +441132068515

Fax: +441132429722

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ABSTRACT

Background: Cyclic vomiting syndrome (CVS) is a functional gastrointestinal disorder (FGID) characterized by intermittent episodes of nausea and vomiting. Our aim was to report its prevalence and associated risk factors.

Methods: Demographic, symptomatic and mood data were collected. Symptoms compatible with CVS were classified as per Rome III criteria. We recorded whether a diagnosis of CVS was considered in patients after negative investigations - "true" CVS. We compared demographics and association with other FGIDs in patients with and without "true" CVS.

Key Results: 920 of 1002 patients completed questionnaire data. We found that of the 920 patients, 112 (12.2%) had symptoms compatible with CVS. 51 of these 112 patients (45.5%) were found to have an organic cause for their symptoms, but 61 patients (54.5%) were deemed to have "true" CVS (prevalence = 6.6%). Common organic causes for symptoms compatible with CVS were gastro-esophageal reflux disease (31.4%), dysmotility (11.4%) and celiac disease (7.8%). Only 34.4% of patients with "true" CVS were asked about vomiting symptoms at their initial consultation, and a diagnosis of CVS was considered in only four (6.6%) of the 61 patients. "True" CVS was associated with younger age, female gender, tobacco smoking and presence of symptoms compatible with other FGIDs ($P < 0.01$).

Conclusions & Inferences: Prevalence of CVS in this outpatient gastroenterology adult population was 6.6%. Identified risk factors included younger age, female gender, tobacco smoking and symptoms compatible with other FGIDs. The condition was considered as a possible diagnosis in <10% of patients who met the diagnostic criteria.

Key words: Vomiting, prevalence, functional gastrointestinal disorders.

Key Points

- Epidemiology of cyclic vomiting syndrome (CVS) in adults is poorly understood. Lack of recognition leads to diagnostic delay, although reasons for this are unclear. We examined these issues in adults in secondary care.
- Approximately 7% of patients in secondary care met criteria for CVS. Symptoms of vomiting were poorly elicited. The diagnosis was considered in a minority.
- Education of physicians likely to encounter patients with CVS is paramount to eliminate diagnostic delay, reduce financial burden and enable appropriate management.

BACKGROUND

Cyclical vomiting syndrome (CVS) is a poorly understood functional gastrointestinal (GI) disorder, which is characterized by acute episodes of nausea and vomiting, followed by asymptomatic periods ranging anywhere from days to months. The condition was first reported in children over 50 years ago[1], and therefore the symptomatology and epidemiology in pediatric populations is well-described.[2-5] However, it is only in the last 20 or 30 years that it has been recognized that this disorder can also present for the first time in later life.[6] The Rome IV criteria for the diagnosis of CVS in adults consists of at least three episodes of acute vomiting in the previous 12 months, lasting less than 1 week, with two episodes in the last 6 months occurring at least 1 week apart, and the absence of vomiting between episodes, although there is a recognition that milder symptoms, such as nausea, may be present in between these episodes.[7]

Despite the development of diagnostic criteria for CVS in adults, the condition remains under-recognized, even though vomiting itself is a common complaint, with up to 3% of individuals reporting it in cross-sectional surveys in the community.[8] The average age of onset of symptoms of CVS in the adult population is 22 years, yet the average age of individuals at the time the diagnosis is made is 31 years.[9] This substantial delay in diagnosis may be due to a lack of recognition of the condition, or a failure to ask pertinent questions when eliciting a clinical history.

Although there are numerous case series of adult patients with CVS,[10-14] the majority of these contain few patients, and therefore the epidemiology of CVS in adults remains poorly understood, with few true prevalence data. There is also a lack of studies reporting associated features or clinical risk factors for the condition. The aims of this study were therefore to estimate the prevalence of CVS in a large number of consecutive unselected referrals with GI

symptoms in secondary care, and to assess the degree to which the possibility of a diagnosis of CVS was considered, as well as to examine associated features in those meeting criteria for CVS, in order to better understand the epidemiology of the condition in adults.

MATERIALS AND METHODS

Participants and Setting

We recruited unselected, consecutive patients aged ≥16 years newly referred from primary care to secondary care for consideration of investigation of GI symptoms. All participants were approached in six of the medical gastroenterology outpatient clinics of Leeds Teaching Hospitals Trust, West Yorkshire, United Kingdom. The hospitals provide secondary care services to a local population of almost 800,000 people in the North of England. The only exclusion criteria were inability to read written English, as the study questionnaires were all self-administered.

Potentially eligible subjects were given a study information sheet at their initial clinic visit, before consultation with a gastroenterologist. Following agreement to participate, written consent was gained from each person. The local ethics committee approved the study (reference 13/YH/0216). Recruitment commenced in January 2014, and continued through to December 2015. During the 2-year recruitment period the six involved clinics saw approximately 2200 new outpatient referrals. As the study was conducted in routine clinical practice, clinical decisions and pathways were not standardized; thus management decisions were based on the clinical expertise and opinion of the responsible gastroenterologist. We did not mandate a minimum panel of blood tests, or upper GI endoscopy and collection of biopsy specimens in all patients. However, all patients agreeing to participate were asked to complete standardized questionnaires detailed below. We have previously used this dataset to examine the performance of the Rome III criteria for irritable bowel syndrome (IBS),[15] to validate a latent class model to predict a diagnosis of IBS,[16] and to validate and modify a scoring system to predict need for random colonic biopsies to detect microscopic colitis in patients with chronic diarrhea.[17]

Data Collection and Synthesis

Demographic, Symptom, Mood, and Somatization Data

Demographic data were collected prospectively and entered into a standardized database; information included gender, age, height (in meters), and weight (in kilograms), from which body mass index (BMI) was calculated, tobacco and alcohol use, marital status, educational status, and ethnicity.

Symptom data were collected prospectively at the initial clinic visit. The Rome III diagnostic questionnaire for adult functional GI disorders was used to collect data on GI symptoms.[18] In addition to this, we recorded if vomiting symptoms were documented as present or absent by the physician in the clinical notes at the initial consultation, and if a diagnosis of CVS was considered by the responsible gastroenterologist in those patients who met the Rome III criteria for the condition.

Mood data were also collected in these patients. We used the validated hospital anxiety and depression scale (HADS).[19] This contains 14 questions; seven relating to anxiety and seven to depression. Each question is scored from 0 to 3, equating to a maximum score of 21. A score of ≥8 was used to identify possible anxiety or depression.

Somatization-type behavior was assessed using the validated patient health questionnaire-15 (PHQ-15).[20] This uses 15 questions, each scoring from 0 to 2, assessing individual somatic symptoms giving a potential maximum score of 30. A score of ≥15 is the validated value to identify high levels of somatization.

All questionnaire data were entered into a database by trained researchers who were not involved in the clinical care of the patient, thus ensuring assessors were blinded to symptom status.

Definition of CVS

Symptoms compatible with a diagnosis of CVS were identified using the scoring system proposed by the validated Rome III questionnaire (Supplementary Table 1).[18] The final diagnosis in each patient was obtained by accessing their clinical records, only after completion of all relevant investigations. A diagnosis of "true" CVS was applied to those individuals meeting the Rome III criteria after appropriate investigations had failed to reveal an organic cause of their symptoms, to the level of investigation deemed appropriate by the responsible gastroenterologist.

Statistical Analysis

We compared demographic data of those with "true" CVS with those of all other patients consulting with GI symptoms using a χ^2 test for categorical data, and an independent samples *t*-test for continuous data, with a mean and standard deviation (SD). Due to multiple comparisons a 2-tailed P value of <0.01 was considered statistically significant for these analyses. All statistical analyses were performed using SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Between January 2014 and December 2015 a total of 1002 patients consented to take part in the study; 638 were female (63.7%) and the mean age of included individuals was 54.4 years (range 16-92 years). Of these patients, 920 (91.8%) provided complete questionnaire data (580 (63.0%) female, mean age 53.9 years (range 16 to 92 years)). In total, 112 (12.2%) of the 920 patients met the Rome III criteria for CVS (Figure 1). However, 51 (45.5%) of these patients had an organic diagnosis that would potentially explain their symptoms, after investigation to the level deemed appropriate by the responsible physician. The commonest or most notable of these are detailed in Table 1, and included erosive esophagitis in 16 patients (31.4%), confirmed dysmotility of the esophagus or stomach in six (11.8%), celiac disease in four (7.8%), peptic ulcer disease in three (5.9%), large hiatus hernia in three (5.9%), esophageal adenocarcinoma in one, and peritoneal metastases in one.

Prevalence of “True” CVS

The remaining 61 (54.5%) patients meeting Rome III criteria for CVS had no organic cause found to explain their GI symptoms, following investigation to a level deemed appropriate by the responsible gastroenterologist. These 61 patients were therefore defined as having “true” CVS, giving a prevalence in this secondary care population of 920 patients of 6.6% (95% confidence interval 5.2% to 8.4%). Only 21 (34.4%) of these 61 patients had any documentation in their clinical notes as to whether vomiting was present or absent at their initial consultation. In addition, a diagnosis of CVS was considered in only four (6.6%) of these 61 patients with “true” CVS.

Features of Patients with "True" CVS

Of the 61 patients deemed to have "true" CVS, 49 (80.3%) were female, and the mean age was 43.6 years. Comparison of those with "true" CVS with all other patients with GI symptoms consulting in secondary care revealed that those with true CVS were significantly younger (Table 2). In addition, there were statistically significant associations between the presence of "true" CVS and female gender, tobacco smoking, and never having married. The reporting of symptoms compatible with other Rome III-defined functional GI disorders, including functional belching, functional chest pain, functional nausea, post-prandial distress syndrome, IBS, chronic proctalgia, and proctalgia fugax was also more likely in those with "true" CVS. Anxiety and somatization scores were significantly higher among patients with "true" CVS, but not depression scores. Finally, there were significantly more individuals with high levels of somatization, and a trend towards more individuals with abnormal levels of anxiety.

DISCUSSION

This study confirms that CVS is prevalent in an outpatient gastroenterology population, with almost 7% of patients seen in a secondary care clinic meeting the Rome III criteria. However, the condition remains under-recognized, with the diagnosis considered in only four (6.6%) of the 61 patients who met these criteria and who were felt to have "true" CVS. Common and notable organic explanations for symptoms in patients who were initially thought to have CVS prior to investigation included erosive esophagitis, esophageal or gastric dysmotility, celiac disease, peptic ulcer disease, and large hiatus hernia. In addition, one patient was found to have esophageal adenocarcinoma, and a second had peritoneal metastases. Younger age, female gender, tobacco smoking, and never having married were all associated with the presence of "true" CVS, anxiety and somatization scores were higher than in other patients with GI symptoms, although no statistically significant difference was seen in depression scores.

We recruited a large number of unselected patients with GI symptoms in secondary care, and none of the physicians consulting in the six outpatient gastroenterology clinics we recruited from has a specialist interest in this area, meaning that our results are likely to be generalizable to other patients seen in outpatient gastroenterology clinics. We collected data concerning a wide range of demographic variables, other GI symptoms, and psychological health, using validated questionnaires, and all patients included were investigated to the level deemed to be appropriate by the responsible gastroenterologist, prior to a diagnosis of "true" CVS being applied.

Weaknesses of the study include the fact that, although we recruited a large sample of patients, the actual number with "true" CVS was small, reflecting that this is a relatively uncommon condition, meaning that we may have lacked sufficient power to detect some genuine associations between CVS and demographics, lifestyle, symptoms compatible with

other functional GI disorders, and mood. In addition, >90% of the patients involved were White Caucasian, meaning that the results of this study cannot be generalized to other ethnicities. We did not mandate a standard level of investigation to exclude an organic cause for symptoms suggestive of CVS, due to the fact that the study was conducted in routine clinical practice. This meant there was no consistent diagnostic algorithm applied to patients to rule out possible organic causes of symptoms prior to a label of "true" CVS being applied. Finally, as studying the prevalence of, and risk factors for, CVS was not the original primary objective of this cross-sectional survey; we did not collect data routinely on other lifestyle choices known to be associated with CVS, such as cannabis use.[21]

Studies from the pediatric literature suggest the prevalence of symptoms meeting criteria for CVS in children and adolescents in the general population are between 0.3% and 1.9%,[4, 22-26] as high as 6.1% in primary care populations,[27] and 8% to 10% in a pediatric gastroenterology clinic.[28] The prevalence in the latter two studies among children is similar to that observed in our study in adults. A study from Ireland estimated the incidence of the condition to be 3.15 per 100,000 children per year.[3] However, CVS is an under-studied disorder in the adult population, and a literature search we conducted revealed no available data on the prevalence of the condition in adults in either the community, or among referral populations, and no studies reporting on risk factors for CVS.

As well as estimating the prevalence of CVS in adult patients in secondary care, our study highlights a failure of gastroenterologists to consider a diagnosis of CVS in the outpatient clinic. Part of this lack of recognition may relate to a failure to ask pertinent questions in the clinical history, as evidenced by the fact that the presence or absence of vomiting as a symptom was recorded in only one-in-three clinical consultations with the patients in this study. Another possible explanation is the observation that symptoms compatible with CVS in our study overlapped with multiple other functional GI disorders, so

it may be that the responsible gastroenterologists were concentrating on other symptoms that they deemed as being more important, or of higher priority, during consultations with these patients. Whatever the reasons, the main findings of our study suggest a need for better recognition of CVS as a potential diagnosis in adult patients with vomiting. The various associations with symptoms of CVS we identified in this study may aid this, and reduce the current diagnostic delay often seen in these patients.

There are other aspects of CVS that we have been unable to examine as part of this study. We did not address underlying pathophysiological mechanisms, another poorly studied area in CVS, although there have been a number of potential theories hypothesized previously. These include activation of the corticotrophin-releasing factor signaling system,[29, 30] abnormal gastric motility,[12, 31] mitochondrial DNA mutations,[32, 33] and other genetic factors including variants in the RYR2 gene, which is involved in stress-induced calcium channels in autonomic neurons,[34] and polymorphisms in genes encoding endogenous cannabinoid and opioid receptors.[35] In addition, we did not evaluate the subsequent management of these patients, an issue that has been highlighted in the literature as problematic for gastroenterologists,[13] although we have reported data from our center regarding the treatment of CVS previously.[36]

In conclusion, the prevalence of CVS among adult patients in secondary care gastroenterology clinics in this study was 6.6%, but the diagnosis was considered in fewer than one-in-ten individuals with typical symptoms, who had no structural explanation for these, and who likely had CVS. Education of gastroenterologists, and other physicians who are likely to encounter such patients, including those in primary care and the emergency department, is paramount in order to eliminate the diagnostic delay seen in adults, and to reduce the financial impact of the condition on both primary and secondary healthcare

services, as well as to institute prompt and appropriate treatment in order to improve quality of life for these patients.

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DISCLOSURES

Guarantor of the article: ACF is guarantor.

Specific author contributions: RCS, RS, DJG, GRL, and ACF conceived and drafted the study. RS, DJG, MJG, and NT collected all data. RCS, GRL, and ACF analyzed and interpreted the data. RCS and ACF drafted the manuscript. All authors have approved the final draft of the manuscript.

Potential competing interests: RCS: none to declare. RS: none to declare. DJG: none to declare. MJG: none to declare. NT: none to declare. GRL: none to declare. ACF: none to declare.

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Table 1. Organic Diagnoses in Patients Meeting Rome III Criteria for CVS.

	Number (%) **(n = 51)**
Erosive esophagitis	16 (31.4%)
Dysmotility	6 (11.8%)
Celiac disease	4 (7.8%)
Peptic ulcer disease	3 (5.9%)
Large hiatus hernia	3 (5.9%)
Esophageal adenocarcinoma	1 (2.0%)
Peritoneal metastases	1 (2.0%)
Other miscellaneous causes	17 (33.3%)

Table 2. Demographics and Baseline Characteristics of Patients with "True" CVS Compared with Patients with Other GI Symptoms not Meeting Criteria for CVS.

	"True" CVS (n = 61)	**Other GI symptoms not meeting criteria for "true" CVS (n = 859)**	**P value***
Mean age in years (SD)	43.6 (17.6)	54.6 (17.3)	<0.001
Mean BMI (SD)	27.2 (8.6)	26.7 (8.1)	0.71
Female gender (%)	49 (80.3)	531 (61.9)	0.004
Tobacco use (%)	25 (41.0)	197 (23.5)	0.002
Alcohol use (%)	32 (53.3)	480 (57.6)	0.52
Marital status (%)			
Married or cohabiting	25 (42.4)	490 (59.3)	
Divorced or separated	9 (15.3)	102 (12.3)	
Never Married	22 (37.3)	150 (18.1)	
Widowed	3 (5.1)	85 (10.3)	0.002
University graduate or postgraduate education (%)	14 (28.0)	161 (20.5)	0.28
White Caucasian ethnicity (%)	54 (90)	777 (91.6)	0.84
Globus (%)	0 (0)	28 (3.3)	0.15
Functional heartburn (%)	19 (33.9)	209 (25.0)	0.14
Functional belching (%)	24 (43.6)	181 (21.9)	<0.001
Functional chest pain (%)	6 (10.5)	22 (2.7)	<0.001
Functional nausea (%)	14 (23.0)	90 (10.6)	0.003
Epigastric pain syndrome (%)	3 (5.0)	18 (2.1)	0.15
Postprandial distress syndrome (%)	34 (63.0)	253 (31.5)	<0.001
Functional abdominal pain (%)	2 (3.4)	15 (1.8)	0.39
IBS (%)	28 (54.9)	186 (23.6)	<0.001
Functional constipation (%)	5 (9.1)	86 (10.8)	0.68

Functional bloating (%)	2 (3.5)	34 (4.2)	0.79
Chronic proctalgia (%)	11 (20.0)	32 (4.1)	<0.001
Proctalgia fugax (%)	25 (45.5)	179 (22.8)	<0.001
HADS anxiety categories (%)			
Normal	21 (40.4)	428 (56.6)	
Borderline	9 (17.3)	145 (19.2)	
Abnormal	22 (42.3)	183 (24.2)	0.01
Mean HADS anxiety scores (SD)	5.7 (4.1)	4.6 (4.2)	0.04
HADS depression categories (%)			
Normal	45 (73.8)	680 (79.2)	
Borderline	10 (16.4)	91 (10.6)	
Abnormal	6 (9.8)	88 (10.2)	0.37
Mean HADS depression scores (SD)	9.2 (5.1)	7.1 (4.7)	0.008
High level of somatization (%)	29 (64.4)	126 (18.8)	<0.001
Mean PHQ-15 scores (SD)	15.6 (5.0)	9.7 (5.5)	<0.001

*P value for independent samples *t*-test for continuous data and Pearson χ^2 for comparison of categorical data.

FIGURE LEGENDS

Figure 1. Flow of Study Participants.