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Clinical, psychiatric and manometric profile of cyclic vomiting syndrome in adults and response to tricyclic therapy[1]

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Abstract *Our goal was to investigate 31 adult patients (mean age 29 years, range 18–62 years) meeting Rome II criteria for cyclic vomiting syndrome (CVS). All subjects completed a clinical questionnaire, a Hamilton Rating Scale for Anxiety (HAM-A) and Zung Depression Inventory. Gastric emptying time was assessed in 30 subjects and electrogastrogram (EGG) in 11 between acute attacks. Twenty-seven patients treated with amitriptyline completed a follow-up questionnaire. The mean age of onset of the patients was 30 years (range 14–53 years) and cycles of nausea and vomiting were accompanied by often-severe epigastric and diffuse abdominal pain. A typical attack ranged from 1 to 14 days, with the majority being 4–6 days. The HAM-A revealed that 84% had an anxiety disorder, and based on Zung Depression Inventory 78% suffered from mild-to-severe depression. Only 4 (13%) patients reported migraine, but 14 had a family history of migraine. Gastric emptying time was rapid in 23 (77%), normal in 4 and delayed in 3. The EGG was abnormal in 7 of 11 patients, with 4 having tachygastria. Of 13 patients using marijuana, 7 had symptom relief, while 2 had resolution of CVS after stopping use. The overall treatment experience in the 24 patients receiving amitriptyline up to 1 mg kg^{-1} day^{-1} for at least 3 months indicated that 93% had decreased symptoms and 26% achieved full remission. Cyclic vomiting syndrome in adults has the following hallmarks: prominence of accompanying abdominal pain and increased prevalence of anxiety and depression, rapid gastric emptying and tachygastric EGG, and successful suppression of attacks by chronic amitriptyline therapy.*

Keywords *abdominal pain, cyclic vomiting syndrome, electrogastrogram, gastric emptying, nausea and vomiting, tricyclic therapy.*

INTRODUCTION

Cyclic vomiting syndrome (CVS) is defined as recurrent episodes of intractable nausea and vomiting with intervals of symptom-free periods.[1] It was first described in the English literature in 1882 by Samuel Gee, who reported a series of nine children ranging from 4 to 8 years of age.[1] Although CVS has been well studied in paediatric populations, its prevalence in adults has been under-appreciated. This illness has four phases[2]: the interepisodic phase, during which the patient is relatively symptom-free; the pre-emesis phase, when the patient begins to sense the approach of an episode and has nausea of varying intensity but is still able to retain oral medications; the emetic phase, characterized by intense, persistent nausea, vomiting and other symptoms; and the recovery period, which begins with the subsidence of nausea and ends when hunger, tolerance of oral intake and vigour return to normal.[3] This syndrome, which affects functioning adults with crippling symptoms of nausea, vomiting and severe

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abdominal pain, is common in all age groups. The length and symptomology of episodes tend to be stereotyped and characteristic for each patient over time.[4]

Unfortunately, patients with these symptoms often go on for years without diagnosis, and both patients and their families suffer a great deal from an impaired quality of their life and economically by failure to maintain their jobs or pay high medical costs in search of answers to their problem. Patients often undergo surgical procedures like cholecystectomy, but their symptoms fail to resolve. The perception that these patients are going to Emergency Departments seeking relief from abdominal pain can result in the label of 'drug-seeking behaviour'. Lack of awareness and understanding of this syndrome among physicians has made it difficult for this group of patients to benefit from any treatment, and so they continue to suffer.

There has been limited knowledge of pathophysiology about this disorder and therefore a paucity of studies describing the spectrum of CVS in adults. We have investigated adult patients who met the Rome II criteria for CVS. Although the Rome II criteria for CVS was designed for the paediatric population, we adopted these criteria as there was no standardized definition for adults and there are many similarities in symptomology among paediatric and adult patients with CVS. Our goals were to identify their clinical characteristics, recognize coexisting diagnoses, document psychiatric status, investigate gastrointestinal motility findings and observe long-term therapeutic outcomes. The broader objectives were to elevate awareness and recognition of this syndrome in adults, offer new insights into medical treatment and provide a basis for more research.

METHODS

From 2004 to 2006, our Motility Center Clinic evaluated 600 patients for symptoms of nausea and vomiting. Thirty-one patients or 5% of this referral base met the Rome II criteria for CVS. This cohort of patients was studied in a 2-year follow-up programme. All patients were asked to complete our CVS questionnaire, which contained 20 questions addressing six areas: (i) epidemiology: sex, age, race and symptomology; (ii) type of symptoms, duration, frequency and intensity; (iii) events preceding the cyclic attacks, e.g. infections, stress and change in bowel habits; (iv) history of migraine, diabetes, irritable bowel syndrome, eating disorders and family history; (v) substance abuse including marijuana; (vi) psychiatric background: depression, anxiety and panic disorder. They all completed a Hamilton Rating Scale for Anxiety (HAM-A),[5] which is a commonly used anxiety rating tool. This clinician-rated symptom scale was designed to qualify the severity of anxiety symptoms and to assess the response to therapeutic interventions. This consists of 14 items, which defined a series of symptoms. Each item is scored on a scale of 0–4. The total score level indicated level of anxiety with <17 mild, 18–24 mild to moderate and 25–30 moderate to severe. Zung Depression Inventory,[6] which identifies the common presentation of depression in an outpatient setting, was also used to determine the prevalence of depression among our subjects. This 20-question inventory is a self-rating questionnaire with each question assigned a score of 1–4, with the highest possible score being 80. A score of 50–69 represents most people with depression. The CVS patients who were identified as depressed by Zung Depression Inventory were further interviewed by the first author (FN), a psychiatrist. DSM-IV criteria were then utilized to grade the severity of depression.

Gastric emptying (GE) was assessed by a 4-h scintigraphic method using a low-fat solid meal.[7] This standardized method for GE consists of a scrambled egg substitute (120 g of free cholesterol and fat-free egg, Sunny Fresh Foods Inc., Monticello, MN, USA) (60 kcal), g jelly (75 kcal) and 120 cc of water. The meal has a total caloric content of 255 kcal (nutritional composition: 72% carbohydrate, 24% protein, 2% fat and 2% fibre). Anterior and posterior images of the stomach were taken immediately after eating, and then hourly for 4 h. Gastric retention of gamma counts was calculated by the Department of Nuclear Medicine, using geometric and decay correction. The values of normal, fast and delayed emptying were based on a multicentre study, which provided GE values in healthy subjects using data obtained in a large sample size with that same meal and methodology.[7] Electrogastrogram (EGG) was recorded in a subgroup of patients between attacks for 30 min in the fasting state and for 60 min after ingestion of a caloric liquid meal (Boost®, Novartis, 360 kcal). Power spectral analysis methods were used to extract quantitative EGG parameters: EGG dominant frequency/power, change in postprandial EGG power, percentages of normal slow waves (2–4 cpm) and dysrhythmias including tachygastria (slow wave frequency >4 cpm) and bradygastria (slow wave frequency <2 cpm) in each recording session.[8]

Amitriptyline was initiated in 27 patients with a starting dose of 25–50 mg. The dose was titrated up to a target dose of 1 mg kg^{-1} day^{-1} over 1–2 months. If patients had side effects, then their dose was reduced. All patients completed a visual analog scale (VAS) before starting treatment and after they have been on

the therapy for a minimum of 3 months. Fifteen of the patients achieved or exceeded 12 months of this therapy (mean 16.8 months, range 12–24 months). Their average daily dose was 75 mg with the range of 50–150 mg. These patients were also evaluated by VAS, which is a well-known scale for assessment of pain. In various studies, it has been shown that VAS is sensitive to change, repeatable and easy to use in experimental and clinical studies.[9–11] Visual analog scale is a horizontal (sometimes vertical) 10 cm line with word anchors at the extremes, such as 'no pain at one end and pain as bad as it could be at the other end'. The patient is asked to make a mark along the line to represent the intensity of their cardinal symptoms of pain, nausea and vomiting. In addition, a subjective assessment of the frequency and severity of nausea, vomiting and abdominal pain was provided by each patient during their treatment trial. This led to a calculation of percentage of subjective improvement for each symptom during treatment.

RESULTS

Thirty-one patients (18 males and 13 females), mean age of 29 years (range 18–62 years), composed the CVS cohort. Their mean age at onset of CVS was 30 years (range 14–58 years). All subjects reported cycles of nausea and vomiting. Epigastric and diffuse abdominal pain of variable severity was also a major component of these cycles among most of the subjects. Patients reported that they had originally lost weight, as much as 10% of their body weight, but later gained and returned to their base line weight. A typical attack, ranged from 1 to 14 days, with the majority having 4–6 days of symptoms. As a self-therapy, 72% reported hot showers; heating pads and lying down in a quiet setting could ameliorate or completely relieve their symptoms. In the Emergency Department, intravenous lorazepam in a dose to induce sleep was the most effective therapy to abort an attack or reduce severity and duration of symptoms. Intravenous ondansetron, phenothiazines and narcotics were often administrated intravenously.

Almost half the number of patients reported that mental stress was a contributory factor for their attacks. However, the results of the HAM-A indicated that 26 (84%) patients were suffering from an anxiety disorder. In addition, the Zung Depression Inventory revealed depression in 24 (78%) patients. By follow-up interview and DSM-IV criteria, they in turn were categorized as: 6 being mild, 15 moderate and 3 with severe levels of depression. A background of migraine headaches or migraines associated with their CVS was noted by only four patients, but a family history of migraine was more common, being reported by 14 patients. Irritable bowel syndrome was observed in 32%, gastro-oesophageal reflux in 19% and a previous cholecystectomy in 23%. The full demographic and clinical characteristics are summarized in Table 1.

Table 1 Demographic and clinical profile

	Male	Female	Total (%)
Number of patients	18	13	31
Irritable bowel syndrome	4	6	10 (32)
Diabetes mellitus	1	1	2 (6)
Cholecystectomy	3	4	7 (23)
Gastro-oesophageal reflux	4	2	6 (19)
Migraine	3	1	4 (13)
Marijuana use	10	3	13 (42)
Depression	14	10	24 (78)
Anxiety	15	11	26 (84)

Thirty patients had GE tests at times of symptomatic quiescence between cycles. Twenty-three patients (77%) had rapid emptying with less than 30% retention at 2 h. Three patients (one diabetic) were delayed with >10% retained after 4 h and four patients (one diabetic) had normal GE. Eleven of the patients had EGG data available and seven were abnormal. The major abnormalities of EGG were tachygastria ($n = 4$) and a decrease in EGG postprandial power change ($n = 6$). Five patients who had symptoms (nausea) during the EGG recording had an abnormal EGG. In comparison with patients who were asymptomatic during the EGG recording, symptomatic patients had significantly more tachygastria (20.4% ± 3.9% *vs* 6.7% ± 2.7%, $P < 0.01$) and significantly less normal slow waves (67.6% ± 2.0% *vs* 86.7% ± 2.8%, $P < 0.05$) in the fed state. The increase in EGG postprandial power in symptomatic patients was also significantly less than that for the asymptomatic group (−2.55 ± 1.01 dB *vs* 1.14 ± 0.54 dB, $P < 0.05$).

Prevalence of marijuana use was sought and 13 admitted daily to weekly use (Table 1). Out of this subgroup, seven regarded marijuana use as therapeutic in improving symptoms, two whose heavy marijuana use dated back to early teenage years reported resolution of symptoms after stopping marijuana, while four did not see any relationship between their marijuana use and their CVS symptoms.

Twenty-seven patients were treated with amitriptyline with a target dose of 1 mg kg^{-1} day^{-1} and all were able to be evaluated by VAS rating after 3 months. Twenty-two patients reported improvement by an average of 5 points in their VAS. Two patients had no

improvement and discontinued the medication on their own. One had significant side effects with hypersomnia and palpitations and also discontinued. Fifteen patients were followed up long enough for them to complete 12 months or more of amitriptyline, with a mean of 16.8 months (range 12–24 months). They achieved a mean daily dose of 75 mg (range 50–150 mg). They had a significant mean improvement ($P < 0.05$) in the severity of their symptoms, measured by VAS of 6.1 points (Table 2; Fig. 1). One of the 15 patients had no improvement before finally discontinuing his treatment. Reductions in pain, nausea and vomiting after amitriptyline were also assessed as a percentage of subjective improvement. Vomiting showed the best degree of improvement (78%), followed by pain (75.3%) and nausea (69.3%) (Table 2; Fig. 2). The overall treatment experience in the 24 patients who received amitriptyline for at least 3 months indicated that 93% had a favourable response with decreased frequency and severity of their symptoms and 26% achieved full remission.

Table 2 Individual patient improvement in symptom severity during treatment with amitriptyline

	Visual analog scale			Subjective improvement (%)		
Patient no.	Before	After	Degree of improvement	Daily nausea	Pain	Vomiting
1	3	8	5	60	80	80
2	2	9	7	80	90	80
3	1	8	7	65	80	90
4	3	8	5	50	50	70
5	1	8	7	60	70	75
6	3	9	6	70	60	80
7	2	10	8	100	100	100
8	2	2	0	0	0	0
9	4	10	6	100	100	100
10	2	8	6	60	70	60
11	1	10	9	100	100	100
12	2	8	6	75	100	100
13	4	9	5	70	80	75
14	3	9	6	50	50	60
15	1	10	9	100	100	100
Mean	2.3	8.4	6.1	69.3	75.3	78

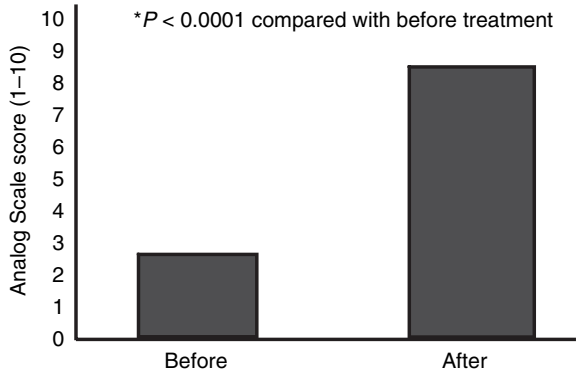

Figure 1 This presents the improvement of cyclic vomiting syndrome symptoms based on visual analog scale score of 1–10, reported by 15 subjects who completed an average of 16.8 months of amitriptyline therapy (1 mg kg^{-1}) and achieved a mean dosing level of 75 mg day^{-1} (data are shown as mean ± 1 SE).

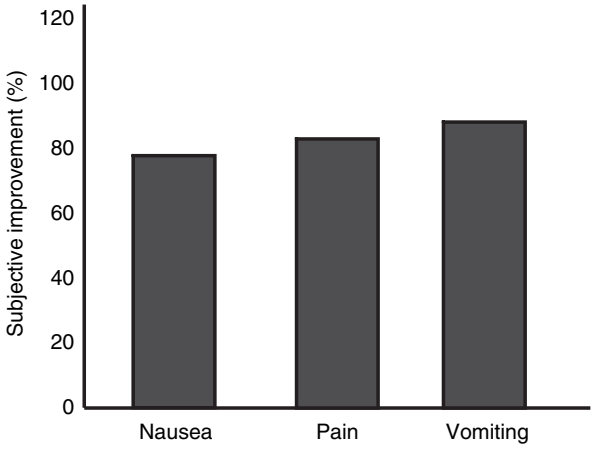

Figure 2 Summary of the percentage of subjective improvement of the symptoms of nausea, vomiting and abdominal pain during amitriptyline (1 mg kg^{-1}), reported as a percentage change by 15 CVS patients who completed an average of 16.8 months and achieved a mean dosing level of 75 mg day^{-1} (data are shown as mean ± SE).

DISCUSSION

Data from our 31 patients with the diagnosis of CVS provides insight into the clinical, psychiatric and manometric characteristics of this syndrome in adults. The most uniform aspect in adults with CVS is the stereotypical nature of the nausea, vomiting and abdominal pain with intermittent symptom-free periods. This phenotype is similar to the paediatric experience.[1,2] The variation in the patients' age, ranging from 18 to 62 years, indicates that many characteristics of CVS are similar irrespective of age at onset of the disorder, suggesting that many unifying aspects may be present in the pathogenesis of this entity.

Depression and anxiety are overwhelmingly a common finding, although it is difficult to distinguish between these psychiatric disorders as being a contributing factor or the result of what can be a stressful and

mood-affecting syndrome. Depression can be a significant comorbidity with CVS, as pain may be exacerbated with somatization disorders that are common both in depression and anxiety. One may also see a resemblance to panic disorder when patients are affected with unpredictable but stereotypic symptoms. These theories are supported by the fact that CVS patients respond well to intravenous lorazepam in their acute attacks.

There is a paucity of data on treatment outcomes in adults. Prakash *et al*., in an open-labelled trial, showed that tricyclic antidepressant therapy (25–50 mg day^{-1}) in 17 CVS patients was associated with complete remission in 17.6% and partial response in 58.8%.[12] In our cohort who could tolerate up to 1 mg kg^{-1} of amitriptyline, 93% of the patients showed a favourable response with decreased frequency and severity of their symptoms: 26% achieving full remission. Patients reported improvement in both psychiatric symptoms and migraine symptoms.[11–13] Tricyclic antidepressants alter autonomic function and therefore can influence the adrenergic abnormalities recognized in some CVS patients.[15] Tricyclic antidepressants, although not classified as antiemetic agents, can influence the afferent pathway involved in central regulation of the vomiting process.[16,17] As tricyclic agents play a favourable role in migraine, depression, anxiety and the abdominal pain associated with irritable bowel syndrome in addition to their antiemetic property, they seem appropriate therapy for the potentially complex pathophysiology of CVS. We conclude that amitriptyline administrated in doses in the higher range is important in improving patients' symptoms over time. The role of psychotherapy and a multidisciplinary approach have also been favourable in children.[18] This approach is yet to be tried in adults and exploring this area in combination with amitriptyline may further increase the remission rate.

The fact that a family history of migraine is prevalent among CVS patients has led to the hypothesis that CVS may be part of the spectrum observed in mitochondrial dysfunction.[19] Inborn genetic disorders of mitochondrial energy metabolism are secondary to mutations in both mitochondrial and nuclear DNA.[20] Mitochondrial DNA mutations have been associated with recurrent episodes of vomiting and migraine. Migraines have been reported to be involved in the pathophysiology of many cases of CVS.[21,22] Elevated body fluid lactate or glutamic and ethylmalonic acids may suggest mitochondrial dysfunction, although these were not specially sought in our patients: conditions that are comorbid with migraine include mood disorders, panic disorder and irritable bowel syndrome.[23,24] These comorbidities were present in our cohort and also including the 41% having a family history of migraine.

Marijuana has also been proposed as a contributing factor in CVS.[25] 'A large number (13 of the 31) of the patients in our group reported daily marijuana use. During follow-up, two patients confirmed resolution of their cycles after they achieved complete abstinence from marijuana, while seven patients claimed that marijuana was actually improving their nausea symptoms. It is difficult to draw conclusions at this time about the role of marijuana. However, the possibility that cannabinoid receptors could be 'saturated' by chronic long-term use of marijuana and that further exposure results in a paradoxic (vomiting) effect could be a consideration. Two of our patients would attest to this concept. Another aspect is that marijuana actually delays GE of a solid meal,'[26] although appetite may be initially increased. Chronic inhibition of GE with marijuana use could predispose a patient to nausea and vomiting, and GE may be inhibited to a greater degree in those CVS individuals with heavy marijuana use.

We have also explored the possibility that there may be an underlying neuromuscular disturbance of gastric function in CVS. This has not been previously broached. Thirty of our patients underwent GE tests with a standardized 4-h scintigraphic methodology using a low-fat solid meal. Twenty-three (77%) patients had very rapid emptying mimicking a 'dumping syndrome' setting. This observation was also made in abstract form by Talley *et al*. in a smaller retrospective series where 17 of 21 (81%) adults with CVS had rapid early-phase GE.[27] These data suggest that CVS patients between acute episodes have a disorder of gastric function. In order to further explore this concept, 11 patients also underwent EGG testing to assess myoelectric activity. Of the 11 patients (64%), seven demonstrated an abnormal EGG. The major electrical abnormality being a dysrhythmia, termed tachygastria, was thought to be increased in settings of nausea and vomiting. One interpretation of the gastric motility data is that the abnormally fast GE would induce a more powerful gastrocolic reflex. We observed irritable bowel syndrome in one third of our patients, and this is consistent with postprandial abdominal discomfort related partly to the gastrocolic reflex. In addition, this gastrocolic reflex could be heightened or exaggerated during anxiety, thus triggering severe abdominal pain and accompanying nausea and vomiting. These data on GE and myoelectric function emphasize a possible role for the stomach in CVS and the influence of brain-gut pathways.

Corticotropin releasing factor (CRF) has been shown to inhibit gut motility and be associated with nausea and vomiting, and may be a factor in vomiting cycles.[28] Corticotropin releasing factor release occurs physiologically with stress and also in the mornings. Many of our patients described a proneness to morning nausea and most attacks began in the early morning hours. The GE and EGG were performed in our patients between acute episodes, but one patient also had a GE during an acute cycle and his emptying was very slow, compared with being rapid when studied during remission. Thus, CRF release during 'stress' or as demonstrated in the high prevalence of anxiety and depression could secondarily inhibit GE and lead to a nausea and vomiting cycle.

Our data describe the spectrum of CVS in adults where this entity is being increasingly recognized. The National CVS Association registry indicated that more adults than children were diagnosed as new cases in 2005. In our Center of Gastrointestinal Nerve and Muscle Function, 5% of patients referred for nausea and vomiting evaluation were diagnosed as CVS. Practising physicians and particularly gastroenterologists should know how to recognize and manage these patients.

In conclusion, our clinical investigation emphasizes the clinical, psychiatric and manometric aspects, and the treatment outcomes for adult CVS patients. The findings highlight the high prevalence of anxiety and depression in this population, and provide the first reports of manometric and myoelectric studies in adult CVS, indicating the presence of a dominant pattern of rapid GE and gastric electrical rhythm abnormalities. The treatment approach suggests that an overall good response can be expected from the long-term use of tricyclic antidepressants. These data provide some hope for this population, although long-term outcomes and the natural history of the entity in adults will require more studies.

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