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REVIEW ARTICLE

Cyclic vomiting syndrome in adults

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Abstract *Cyclic vomiting syndrome (CVS) was initially described in children but can occur in all age groups. Cyclic vomiting syndrome is increasingly recognized in adults. However, the lack of awareness of CVS in adults has led to small numbers of diagnosed patients and a paucity of published data on the causes, diagnosis and management of CVS in adults. This article is a state-of-knowledge overview on CVS in adults and is intended to provide a framework for management and further investigations into CVS in adults.*

Keywords *cyclic vomiting syndrome, dyspepsia, gastroparesis.*

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INTRODUCTION

Cyclic vomiting syndrome (CVS) is a disorder characterized by recurrent episodes of severe nausea and vomiting interspersed with symptom-free periods. This syndrome was first described in the English literature in 1882 by Samuel Gee[1] who reported a series of nine children ranging from 4 to 8 years in age. While CVS has been studied in paediatric populations,[2,3] its occurrence in adults has been underappreciated. It is now apparent that this disabling illness affects all ages, including young and middle aged adults. Knowledge about CVS in adults is more limited than in children and generally is based on retrospective case series. Although the disorder in children and adults probably represents a continuum, some evidence suggests there may be differences in paediatric and adult CVS in terms of symptom profiles, pathogenesis and associated comorbidities (Table 1). Indeed, in contrast to most childhood cases, a subset of adult patients develops a CVS-like disorder which is secondary to other chronic systemic diseases or, in some cases, appears to be associated with substance abuse.

Table 1 Comparison of adults and children with cyclic vomiting syndrome

	Children	Adults
Age at diagnosis	4.6–5.3 years	34.8 years
Delay in diagnosis	2.6–3.1 years	7.9 years
Duration of episodes	2.0 days	3.8 days
Interepisode intervals	1.0–3.1 months	3.0 months
Prodrome	Common	Common
Symptoms during episode		
Vomiting	Universal	Universal
Abdominal pain	Common (72–80%)	Common (58–71%)
UGI complications	Common (22–32%)	Common (38%)
Interepisodic nausea or dyspepsia	Rare	Common
Associated psychiatric manifestations	Common	Common
Migraine headache or family history of migraine headache	Common (39–82%)	Common (24–70%)
Mitochondrial DNA disorders	Reported	Not reported
Disorders of fatty acid metabolism	Rare	Not reported
Cannabis abuse	Not reported	Reported

Data from Fleisher and Matar[3], Fleisher *et al.*[10], Prakash *et al.*[11], Namin *et al.*[14] and Li and Balint[6].

This manuscript is intended for two purposes. The first is to provide an overview of CVS in adults and a framework of the disorder for adult and paediatric gastroenterologists, gastrointestinal (GI) motility specialists, internists, neurologists, psychologists and basic scientists. The second is to introduce the disorder, the diagnostic criteria, management and current theories of pathogenesis to clinicians and scientists who diagnose, manage and investigate these patients. This article, in part, was derived from the proceedings of two expert panel meetings on adult CVS sponsored by the Cyclic Vomiting Syndrome Association (CVSA) and the American Neurogastroenterology and Motility Society: (i) CVS Across the Ages; June 3–4, 2006 at the Medical College of Wisconsin and CVS in Adults; (ii) September 17, 2006 in Boston, MA at the American Neurogastroenterology and Motility Society Meeting.

CLINICAL PRESENTATION AND SPECTRUM

Clinical symptoms of CVS in children

Large databases of paediatric patients with CVS maintained by Chong in England (108 patients) and Li in the USA (463 patients) provide remarkably similar clinical descriptions of paediatric patients with CVS.[4–6] Discrete vomiting episodes lasting from 2 h to 10 days occur in 93–100% of children and are accompanied by symptoms of nausea, retching and abdominal pain in four-fifths of patients. Common triggering factors include stress, emotional excitement and infections. The episodes are severe with at least four emeses per hour when at its worse in 71–77% of patients. Abdominal pain accompanies these episodes in 67–80% of patients. Affected children generally have four to 12 episodes per year. Between episodes, the majority of children (63–94%) are well; however in the UK study, more than one-third of patients are not symptom free in between episodes, suggesting a heterogeneous aetiology or a coalescing syndrome. The average age at initial diagnosis is 5 years of age, however, this diagnosis is typically delayed for several years.[6] A family history of migraine is present in 67–82% of cases.[5] This paediatric presentation is well described in previous reviews[3,6] and listed in Table 1. Paediatric CVS has been reported to have a prevalence of 0.04–1.9% of children[7,8] with an incidence of new cases to be approximately 3 per 100 000 children per year.[9] The natural history of CVS in children is variable: some patients will ultimately cease to have emetic episodes, some switch from having vomiting episodes to having migraine headaches, whereas some continue to have vomiting episodes.[7,8]

Clinical symptoms and epidemiology of CVS in adults

As in children, adults with CVS experience multiple episodes of vomiting with frequent visits to Emergency Departments (EDs) for relief of nausea, vomiting and resultant dehydration. Table 1 compares the characteristics of adults and children with CVS. Episodes are accompanied by severe abdominal pain in approximately 58–71% of adult patients.[10,11] Triggers of acute emetic episodes are similar for adults and children

with CVS and include infections (e.g. chronic sinusitis and other upper respiratory infections), psychological stress, motion sickness, lack of sleep, physical exhaustion and certain food products (e.g. chocolate, cheese, monosodium glutamate).[12,13] In some women, episodes also can be triggered by menses – a phenomenon termed catamenial CVS. Adult patients with CVS often remain undiagnosed for some time due to a lack of recognition of this clinical entity with reports suggesting a delay in diagnosis for up to 8–21 years following disease onset.[10,11] In emergency rooms, patients may be presumed to have viral gastroenteritis or food poisoning. Some patients are thought to have gastroparesis, a disorder typified by chronic nausea and vomiting. In one study, 5% of patients referred to a major medical centre for evaluation of gastroparesis had CVS.[14] Patients who are undiagnosed are sometimes subjected to surgery that usually does not alter the course of their illness. Thirty-nine per cent of a series of 41 adults with undiagnosed CVS underwent one or more surgical procedures (most commonly cholecystectomy).[10] Other patients are speculated to have psychiatric disorders such as conversion disorder, eating disorders, or personality disorders to explain their unusual symptom presentations. Some patients may be suspected or accused of being drug seeking because narcotics are often given for the abdominal pain in the ED. Finally, the lack of a diagnosis and appropriate treatment programmes result in many patients with CVS experiencing severely impaired quality of life due to the repeated episodes of vomiting, emergency intervention and hospitalization. Both patients and their families often suffer economically and socially when the symptoms interfere with day-to-day life including education, job performance and marriage. Disability is commonly associated with adult onset CVS.

Cyclic vomiting episodes are stereotypic for each individual patient and characterized by four phases in many adults:[10,11]

1 The interepisodic 'well phase' occurs between vomiting episodes when the patient is relatively symptom-free. This phase typically last weeks to months.
2 The pre-emetic or 'prodromal phase' occurs when the patient begins to sense the approach of an episode but may still be able to keep down oral medications. The usual prodromal symptom is nausea of varying intensity, but may include abdominal pain, lethargy, anorexia and pallor. This phase lasts minutes to hours.
3 The 'emetic phase' is characterized by intense, persistent nausea, repeated vomiting and other symptoms (pallor, abdominal pain, prostration and listlessness). This phase lasts from hours to days.
4 The 'recovery phase' begins with termination of vomiting and ends when hunger, tolerance of oral intake and vigour returns.

Criteria for the diagnosis of CVS in adults were published by the Rome III working teams on functional GI disorders in 2006 (Table 2).[15] There have been several case series reported in the literature describing the demographic, clinical and psychological characteristics of adult patients (ages 18–62 years) with CVS (Table 3).[10,11,14,16,17] In a series of 41 adult patients with CVS, Fleisher *et al.*[10] found the age of onset of symptoms ranged from 2 to 49 years and the delay in diagnosis from onset of symptoms averaged 21 years.

Table 2 Rome III diagnostic criteria for cyclic vomiting syndrome in adults

The following three criteria must be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis
1 Stereotypical episodes of vomiting regarding onset [acute and duration (less than 1 week]
2 Three or more discrete episodes in the prior year
3 Absence of nausea and vomiting between episodes
Supportive criteria for the diagnosis of cyclic vomiting syndrome includes personal or family history of migraine headaches. *Source*: Ref. 15.

Table 3 Published studies of cyclic vomiting syndrome in adults

Author (reference)	Year and type of publication	No. adults	Age at onset of Sx average (range)	Attack duration	Frequency of attacks
Abell *et al.*[17]	1988 (manuscript)	8 (5M, 3F)	NR	3.5 days	3.2 months
Prakash *et al.*[11]	2001 (manuscript)	21 (9M, 12F)	34.8 ± 3.8 years	3.8 ± 0.4 days	3.1 ± 0.4 months
Fajardo *et al.*[16]	2005 (abstract)	50 (28M, 22F)	NR	NR	NR
Fleisher *et al.*[10]	2006 (manuscript)	41 (24M, 17F)	21 (2–49) years	3–4 days	NR
Namin *et al.*[14]	2007 (manuscript)	31 (18M, 13F)	30 (14–53) years	5 (1–14) days	NR

NR, not reported.

In parallel to findings in children, 70% of adults in his case series reported migraine headaches between or during episodes and psychological disturbances such as panic attacks were common (Table 1). However, in contrast to classic paediatric patients with CVS, 50–63% of adult patients with CVS experienced interepisodic nausea. In another case series, the most consistent findings were the stereotypical nature of the attacks of nausea, vomiting and abdominal pain between symptom-free periods.[14] These characteristics are similar to CVS in children, although the episode duration appears to be more prolonged (3–6 days) in adults.[3,11]

Recent published observations in adults and unpublished ones in children indicate that some patients can progress from a pattern of discrete emetic episodes to a pattern of nearly continuous nausea and vomiting.[10] This form of disease, termed 'coalescent CVS', appears to be more common in adults than in children. These patients suffer subacute symptoms of nearly continuous nausea and frequent emesis lasting weeks to months that can result in profound weight loss requiring special nutritional support. 'Coalescent' patients are usually unable to work or attend school. One-third of a series of 41 adults were disabled and required financial support.[10] As coalescence is most often observed in patients with untreated CVS, it may represent an evolving form of CVS. When appropriate treatment interventions are pursued, or treatment is optimized, many patients improve but the cause of this disorder and whether the pathophysiology of this disorder differs from the more typical CVS with well episodes between ill episodes, is unclear.

A cyclic pattern of symptoms may occur in some individuals who do not meet strict criteria for CVS, but nevertheless may have discrete exacerbation of symptoms. A subset of individuals with diabetes mellitus experiences episodic vomiting with symptom free intervals as in CVS.[18] In addition, another subgroup of diabetic patients with documented gastroparesis also report cyclic episodes of vomiting, and meet the criteria for both conditions. Abdominal pain with or without diarrhoea can also precede the onset of vomiting, suggesting a CVS-like disorder may be a manifestation of severe irritable bowel syndrome. Another variant of CVS presents with recurrent morning nausea with limited vomiting which resolve later in the day, permitting normal functioning and food intake. These patients may never achieve a full blown attack requiring admission.

A rare syndrome of recurrent vomiting associated with hypertension and profound listlessness during episodes has been reported in children with CVS-like conditions by Sato *et al.*[19–21] Similarly, Pasricha *et al.*[22] have described an adult with cyclic vomiting episodes associated with hypertension and depression during the episodes.

Associated conditions/comorbidities and complications of CVS

Conditions observed to co-exist in adults with CVS include migraine headaches, psychiatric disease, chronic marijuana use, gastro-oesophageal reflux disease, irritable bowel syndrome, gallbladder disease and insulin-dependent diabetes mellitus.

Migraine headache Migraine headaches and/or a family history of migraines are present in 39–82% of children with CVS and 24–70% of adults with CVS.[2,11] Migraine headaches occur commonly in adult patients with CVS whereas many children have not yet developed them. Migraines may develop in children with CVS as they reach adolescence, with associated loss of the emetic disorder. Some adults may give a remote history of migraine, but do not currently experience headaches. In addition, a family history of migraine is also prevalent among patients with CVS who themselves may not have migraine.[2,23] This association between migraine and CVS was first suggested by Whitney in 1898 and has since been confirmed in multiple studies that have further observed homology of symptoms during CVS and migraine episodes (e.g. pallor, lethargy, nausea, abdominal pain), stereotypy of attacks and the high prevalence of familial migraines in both disorders (up to 72%).[2] The family history of migraine in patients with CVS is particularly prominent in the maternal lineage. As will be discussed, the maternal inheritance pattern of migraines and CVS suggest that CVS may be in part inherited through mitochondrial DNA (mtDNA).[24]

Migraine headache, abdominal migraine and CVS are functional disorders that seem to be manifestations of a common diathesis. Each is characterized by stereotypic, self-limited episodes. Patients often experience symptoms of the other two disorders. Their nosological distinction is based on their predominant symptoms: headache in migraine, intense abdominal pain in abdominal migraine, and nausea and vomiting in CVS.[22] The prevalences of CVS, abdominal migraine and migraine headaches peak at ages 5, 10 and 11 years respectively.[7] Individual patients may progress from one disorder to the others over time. The efficacy of antimigraine medications including amitriptyline, cyproheptadine, propranolol and sumatriptan, as prophylactic medications or to attenuate the severity and

duration of cyclic vomiting episodes supports a common pathogenic link with migraines.[2,25]

Despite the common association of CVS with migraine, CVS in children and adults is more than a migraine variant as migraine headaches are not present in all patients. Eighteen per cent of the paediatric series reported by Li *et al.*[2] had no evidence of a migraine diathesis. These individuals tended to have longer vomiting episodes and responded less well to antimigraine medications, suggesting different underlying mechanisms of disease in those with and without associated migraine.

Psychiatric disease Psychiatric disorders, including anxiety and depression, are frequent comorbid findings in patients with CVS.[26] In individual cases, it is difficult to distinguish whether these conditions are contributing factors towards the development of vomiting episodes, the result of coping with an unexplained and distressing illness, or whether common underlying pathogenic factors predispose patients to both vomiting episodes and psychiatric conditions. Findings support the perception that CVS is not psychologically driven (psychogenic), but rather is a primary disorder, associated with psychological comorbidity.[27]

There may be a subset of patients where CVS is a manifestation of extreme anxiety, panic or unstable mood. Panic disorder may be present in CVS and panic attacks are anecdotally reported to trigger attacks in two-thirds of adults.[10] Identification and treatment of panic disorder in patients with CVS can lead to a reduction in CVS attacks.[28] Therefore, it seems appropriate that clinicians consider panic disorder when evaluating patients with CVS-like symptoms.

Marijuana use Marijuana use has been proposed as a contributing factor in some patients with CVS.[29,30] On the other hand, marijuana is also used by patients to reduce the nausea and vomiting. Allen *et al.*[29] initially described nine patients with a history of prolonged cannabis abuse, predating the onset of the vomiting illness. Hyperemesis followed a cyclical pattern every few weeks or months, against a background of habitual cannabis abuse and the taking of frequent warm showers. Cessation of cannabis led to termination of the cyclic emesis. In another series of adult patients with CVS,[14] a large number (13 of 31) of patients reported daily marijuana use, but during follow-up, only two patients that ceased marijuana use had resolution of their vomiting cycles, whereas seven claimed that marijuana improved their nausea, lessened anxiety and hastened the return of normal appetite during the recovery period. The role of marijuana as a causative or treatment agent in CVS remains unclear. It is unknown if chronic marijuana use has deleterious effects on the endogenous cannabinoid system or if other constituents of the inhaled smoke from marijuana cigarettes accumulate in toxic quantities.

PATHOGENESIS AND PATHOPHYSIOLOGY OF CVS

Scientific and therapeutic investigations have yet to clarify the aetiopathogenesis of CVS. The recent recognition of the disease as an entity has led to increasing interest in the cause of this disorder. Cyclic vomiting syndrome has only recently been recognized to occur in adults. Rigorous scientific and therapeutic investigations have been difficult to perform as most centres may only have identified a few cases. Multicentre studies are difficult due to the acuity of the disease.

There is an emerging consensus that CVS appears to involve dysregulated central neural pathways and neuro-endocrine mediators involved in the afferent and efferent brain–gut pathways of nausea and vomiting.[31] Despite an incomplete understanding of the mechanisms underlying this dysregulation, important advances are being made in the clinical understanding of this disorder which may open the way for new treatments. Several pieces of evidence from different lines of investigation point towards an important role of altered brain responses to visceral and to emotional stimuli. Evidence has accumulated which suggest additional pathogenic roles for autonomic, GI, central neuroendocrine and mitochondrial metabolic factors.

One proposed model attempts to integrate the various systems and pathways suggested to be involved in CVS. This model suggests that common triggering stressors (e.g. psychological, infectious) initiate the vomiting cascade in subjects with specific susceptibility factors (e.g. family history of migraines, autonomic and GI dysfunction, energy deficits due to mitochondrial dysfunction) that render affected individuals to respond with repeated episodes of emesis. The defect that enables this cascade to feed forward for hours to days is unknown.

Possible pathophysiology of CVS

Triggering events Psychological or infectious stressors are well known to initiate central arousal and the cascade of hypothalamic-pituitary-adrenal (HPA) axis activation. Specifically, the corticotropin-releasing factor (CRF) signalling system is activated by stressors (e.g. infections, psychological, energy depletion) and plays an important role in mediating autonomic

(sympathetic activation and vagal inhibition) alterations that impact on gut motility.[32–34] It is well recognized that various immunological, psychological or physical stress can precipitate the episodic occurrence of emesis in 70% of children with CVS.[8] During the past decade, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies have helped identify and define central nervous system abnormalities in patients with functional GI disorders[35] including CVS.[36] Although inconsistencies have been observed across different studies, there is converging evidence of altered responsiveness of central arousal circuits involving the amygdala, cingulate cortical subregions and pontine regions, including the peri-aqueductal grey region and the locus ceruleus complex.[37] It appears that several functional GI disorders and other stress-sensitive disorders, such as migraine headaches, share altered responsiveness and modulation of central arousal circuits, including dysregulation of the periaqueductal grey (PAG) area. Preliminary results from functional[15] O-PET brain imaging in adult patients with CVS suggest alterations in brain areas that deal with heightened awareness and anxiety (the cingulated cortices) as well as those that deal with pain and pleasure (the inferior frontal cortex).[36]

Susceptibility factors The linkage between CVS and 'migraine headaches' may indicate that migraines are either an important factor in CVS pathogenesis or merely a marker for a more generalized underlying central nervous system disorder. Migraine headaches involve both an electrophysiological event (spreading depression) that corresponds to the clinical visual aura and a cerebrovascular event with vascular dilation that causes pain and further neural activation.[38] In some patients with a haemiplegic form of migraine, an ion channelopathy, neuronal P/Q type calcium channel associated with a CACNA1A gene mutation, increases neuronal sensitivity to depolarization.[39] Recent neuroimaging studies have identified the locus of migraine activation in the brainstem. In one study, increased blood flow in the cingulate, auditory and visual cortices observed on PET scanning were reversed by the antimigraine drug sumatriptan ($5HT_{1B/1D}$ agonist), whereas brainstem activation patterns were not affected.[40] Similarly, in a second study on migraine and cluster headaches, initial rostral brainstem activation was unaffected by sumatriptan.[41] The importance of altered brainstem activation in patients with CVS is unexplored.

The 'autonomic nervous system' plays a prominent role in the responses to a range of emetic activators. An integrated series of brainstem nuclei receives input from vagal and sympathetic afferent nerves during emetic stimulation. Efferent signals are then generated in the brainstem nuclei which initiate the stereotypic and coordinated muscular actions involved in vomiting. Using several tests of autonomic function including postural adjustment ratio, heart rate variability, tilt table and sudomotor testing, three groups of investigators have observed increases in sympathetic tone in children with CVS.[42–44] The most common shared finding in these reports was an adrenergic abnormality, but co-existent vagal cholinergic function abnormalities was reported. Comorbid dysautonomic symptoms commonly experienced by patients with CVS include migraine headaches, gut dysmotility, complex regional pain syndrome and postural orthostatic tachycardia syndrome (POTS).[45] Based on these studies describing dysautonomic features in patients with CVS, investigators have hypothesized that sympathetic autonomic imbalance may render patients more susceptible to over-respond to central emetic signals.

'Gastric emptying' and myoelectric activity have been investigated in adult patients with CVS, primarily during asymptomatic periods between emetic episodes. Two groups have documented the presence of rapid gastric emptying between attacks in adults with CVS.[14,16] In contrast, delayed gastric emptying during the vomiting phase was observed in some patients when this test was able to be performed.[14] The delay in gastric emptying during the symptomatic phase may represent a generalized response to central nausea, whereas rapid gastric emptying in the vomiting-free period may indicate that there is an underlying autonomic dysfunction as described above. Electrogastrography (EGG) of patients with CVS demonstrates prominent tachygastria and blunting of the amplitude of waves in response to meal ingestion[14,17,46] similar to findings in individuals with idiopathic nausea and vomiting syndromes. This may relate to the occurrence of coalescent nausea between vomiting episodes. Small bowel dysmotility has also been reported in patients with CVS.[17]

Cellular energy deficits resulting from 'mitochondrial dysfunction' may contribute to the autonomic dysfunction of CVS that could be present in patients with CVS. As mitochondrial energy production is a ubiquitous cellular function, mitochondriopathies have a range of clinical presentations. Because of high cellular energy demands, disorders of nerve and muscle function are especially common.[47] Defects in mitochondrial energy production due to mutations may predispose individuals to the onset of vomiting during periods of heightened demands for energy (e.g. stress,

infections). The strong maternal bias of migraine and other functional or dysautonomic conditions in CVS kindreds suggests that mtDNA alterations (sequence variations) could be contributing factors in the pathogenesis of CVS (and migraine) in some patients.[2,24,48–50] Mitochondrial DNA is comprised 37 genes which are involved in energy metabolism and, unlike nuclear DNA, is only maternally inherited without recombination, and therefore affecting the entire matrilineage (individuals related entirely through women).[47] Disordered mitochondrial metabolism during emetic episodes is evidenced by elevated urinary organic acids (e.g. Krebs cycle intermediates, dicarboxylic acids) in patients with CVS similar to that seen in patients with known mitochondrial disorders.[24,49] As in mitochondrial disorders, treatment with intravenous dextrose appears to help relieve symptoms in up to half of patients with CVS during an episode, suggesting that the dextrose helped to alleviate the energy deficit due to the underlying mitochondrial defect.[6,50] Recent studies characterized heteroplasmic mutations (i.e. two species of mtDNA present in the sample) and CVS and migraine-associated homoplasmic polymorphisms in the small (1 kDa) mtDNA control region of a subset of children with CVS.[51–53]

Mediators and pathways Potential neuroendocrine mediators such as CRF and related downstream effector pathways – cortisol production and prostaglandins E_2 – as well as autonomic alterations may participate in initiating or sustaining vomiting in CVS.

The classic function of CRF is to stimulate adrenocorticotropic hormone (ACTH) production by the anterior pituitary, thereby activating the HPA axis and the stress response. In addition, CRF appears to mediate anxiogenic, autonomic (sympathetic activation, vagal inhibition and sacral parasympathetic activation), and visceral (inhibition of gastric transit and stimulation of colonic secretory and motor function) responses to stress. Experimental studies show that CRF pathways are activated by psychological or immune (elevated levels of cytokines) stressors that induce catecholamine release and reduced vagal efferent activity that lead to hypertension and gastric stasis; these responses can be prevented by CRF receptor antagonists.[54] Taché[34] has proposed that altered CRF receptor-mediated signalling plays a key role in triggering emesis in patients with CVS. This concept is supported by the similarity between clinical, endocrine, autonomic features in patients with CVS and those elicited by brain CRF hyperactivity.[34] Interestingly, tricyclic antidepressants (TCAs) reduce frequency of vomiting episodes and inhibit the promoter activity of the CRF gene.[34,55,56] A preliminary study reports elevated peripheral CRF levels in affected children during active vomiting episodes.[57] However, definitive proof of concept will require therapeutic benefits of, as of yet unavailable, CRF receptor antagonists in the treatment of CVS episodes.

'Prostaglandin' pathways are activated by CRF and can exert a positive feedback to induce CRF release.[58,59] The recruitment of CRF pathways can be inferred from Sato *et al.*'s[19] initial report describing overactivation of the HPA axis with development of transient hypertension in a subset of children with CVS (Sato variant). They found a rise in peripheral levels of ACTH, cortisol, catecholamines (noradrenaline and adrenaline), antidiuretic hormone (ADH) and prostaglandin E_2 (PGE_2) preceding and during the early part of the vomiting episode. The importance of catecholamine and prostaglandin pathways in the genesis of this variant is evidenced by the reduction in symptom produced by the α-adrenoceptor agonist clonidine and the prevention of vomiting episodes by indomethacin pretreatment.[19–21] In 1964, Wolff *et al.*[60] described a patient with cyclic nausea and vomiting associated with hypertension, abnormal glucose tolerance, elevated plasma ACTH and cortisol that could be attenuated by high doses of dexamethasone. Underlying hypothalamic derangements have also been suggested in other paediatric CVS cases.[61] Similarly, Pasricha *et al.* describe an adult with CVS with elevations in ACTH and cortisol preceding the attacks of vomiting. Emetic episodes in this patient were reduced by the non-steriodal agent ketorolac, raising the possibility that both HPA axis derangement as well as endogenous prostaglandin release participate in symptom generation.[22]

DIAGNOSTIC TESTING FOR ADULTS WITH PRESUMED CVS

The differential diagnosis of clinical disorders that can mimic CVS is extensive and includes GI infections and inflammatory conditions, disorders of gut motor function, eosinophilic oesophagitis or gastroenteritis, hepatopancreaticobiliary disorders, surgically remediable intra-abdominal abnormalities including bowel obstruction, as well as a range of extra-abdominal disorders including ureteropelvic junction obstruction.[62,63] The initial evaluation of the patient with presumed CVS should exclude these conditions.[64,65] Table 4 lists disorders to exclude when considering CVS in adult patients and the appropriate test to evaluate for the disorders. Once a positive diagnosis of

Table 4 Disorders that mimic cyclic vomiting syndrome in adults

Disorder	Appropriate test to evaluate for this disorder
Gastrointestinal disorders	
Gastric disorders	
Peptic ulcer disease	Upper endoscopy
Gastroparesis gastric	Emptying test
Gallbladder disorders	
Cholecystitis	Abdominal ultrasound
Biliary tract dysmotility	HIDA scintigraphic imaging
Small bowel disorders	
Intermittent small bowel obstruction	Abdominal CT scan (CT enterography)
Chronic intestinal pseudo-obstruction	Abdominal obstruction radiographic series
Malrotation with volvulus	Upper gastrointestinal with small bowel follow through
Extra-intestinal disorders	
Central nervous system abnormalities	Head magnetic resonance imaging
Mass	
Hydrocephalus	
Renal disorders	
Nephrolithiasis	Urinalysis
Ureteropelvic junction obstruction	Renal ultrasound
Hormonal and metabolic disorders	
Adrenocortocoid insufficiency	Plasma cortisol
Acute intermittent porphyria	Urinary porphyrins

CVS is made by the characterization of the typical clinical presentation and by the exclusion of other disorders, subsequent diagnostic investigations generally are restricted to those tests that facilitate detection of the complications of CVS including electrolyte abnormalities, dehydration and GI haemorrhage.

Typical initial screening testing includes laboratory tests (complete blood count and differential, glucose, electrolytes, liver chemistries, pancreatic enzymes and pregnancy test), urinalysis, and plain flat and upright radiographic series to exclude abdominal obstruction. It must be recognized that CVS can produce misleading laboratory findings in some cases. For example, neutrophilia without band forms can be caused by stress-induced leucocyte demargination. Lactic acidosis and ketosis are sequelae of prolonged vomiting and fasting. High urine specific gravity, often found with profound dehydration, may be elevated instead as a result of increased ADH production resulting from the patient's nausea. Hyponatraemia with fluid retention can occur in some patients with the Sato variant of CVS.[20]

The decision to perform additional testing must be tailored to the individual patient presentation – the history and physical examination with particular attention to alarm findings including haematemesis, pronounced abdominal tenderness with guarding or rebound and neurological abnormalities such as altered consciousness and lateralizing neurological findings.[64] In many instances, it may be appropriate to consider other tests including upper GI contrast radiography, upper endoscopy, abdominal CT scanning or ultrasonography, and brain imaging with MRI to exclude structural lesions of the brain, especially in the posterior fossa. Endoscopy is considered for haematemesis, which can be a consequence of the vomiting either from a Mallory–Weiss tear or from prolapse gastropathy in which the gastric cardia is forced into the distal oesophagus by violent retching. In paediatric patients, a renal ultrasound is often performed to evaluate for hydronephrosis from ureteropelvic junction obstruction (Table 4). In adults, consideration often is given to gastroparesis as an alternate diagnosis. Indeed, a subset of patients with diabetic gastroparesis presents with cyclic emetic episodes similar to CVS.[18,66] These individuals exhibit more severe gastric retention than those with chronic symptoms. However, as observed in recent studies, rates of gastric emptying often are accelerated rather than delayed in patients with CVS during the asymptomatic period when vomiting is absent allowing the test to be performed.[14,16]

Although metabolic disorders are more commonly detected in children, if episodes are precipitated by high protein meals, or if the patient suffers from a comorbid neuromuscular condition, then evaluation is performed to exclude metabolic disorders including disorders of fatty acid oxidation (e.g. medium chain acyl CoA dehydrogenase deficiency), mitochondriopathies, urea cycle defects (e.g. partial ornithine transcarbamylase deficiency), acute intermittent porphyria (in adolescents and adults) and disorders of ketolysis. Similarly, endocrine evaluation for Addison disease by measurement of a morning cortisol might be considered.[62] Blood tests to be obtained in this patient subset may include glucose (hypo-or hyperglycaemia), electrolytes (especially for the anion gap), lactic acid levels, ammonia (to detect partial urea cycle enzyme deficiencies and other conditions), fasting morning cortisol, quantitative amino acid levels, carnitine, an acylcarnitine profile and mtDNA analysis (including testing for 3243A → G and large rearrangements). In general, blood and urine samples (ketones, organic acids, carnitines and a porphyria screen) are optimally obtained before giving i.v. dextrose.[67]

In a study of 225 children with episodes of cyclic vomiting, 49% had an identified disorder other than CVS that either caused or contributed to the vomiting.[62] In 12%, a serious surgical disorder was found in the GI tract (malrotation), kidney (acute hydroureter), or central nervous system (neoplasm). In 2%, Addison's disease and metabolic disorders (disorders of fatty acid metabolism) were found. Although 41% of children with CVS had associated disorders that could potentially contribute to the vomiting (mild oesophagitis and chronic sinusitis), these were generally not thought to be the cause based upon lack of response to treatment. In this series, the tests with the highest yield were endoscopy, sinus films and small bowel radiography. Laboratory studies to screen for metabolic or endocrine abnormalities were best performed during the episodes to maximize the chance of detection of potentially aetiological disorders.

Even though a comprehensive diagnostic evaluation may be indicated in selected patients, the clinician should be aware that most testing in patients with idiopathic CVS symptoms will be negative.[10] Recent cost-effectiveness modelling studies in children suggest that it is most cost-effective to begin prophylactic treatment in otherwise typical patients rather than perform an extensive battery of tests.[68] The most cost-effective management strategy was to image the upper GI tract and small bowel through a barium series to exclude malrotation followed by empiric antimigraine therapy – this approach reduced costs by nearly half to $1600 and reduced the number of upper endoscopies performed by nearly two-thirds.

TREATMENT

Treatment of CVS in adults remains largely empiric because of its elusive pathogenesis and the paucity of controlled therapeutic trials.[69] The overall approach to treating a patient with CVS should include the consideration of lifestyle modifications such as avoidance of triggering factors, prophylactic drug therapy to prevent recurrent episodes, abortive treatment and/or supportive care to ameliorate acute episodes, and psychological support of the patients and family. These recommendations are based on open label trials reported in case series and not generally on more rigorous prospective clinical trials.

A placebo response rate of up to 70% in patients with CVS has been reported following detailed consultation and diagnosis alone without initiation of pharmacotherapy.[10] Another confounding variable in the treatment is the heterogeneity of CVS that has been observed in children, but likely also is present in adults. Cyclic vomiting syndrome subgroups include: (i) those with migraine; (ii) hypertension during episodes (Sato variant); (iii) catamenial CVS; (iv) diabetes subgroup; (v) those with co-existing neuromuscular disorders (CVS plus);[45] (vi) association with extreme anxiety; (vii) morning nausea and/or vomiting only; and (viii) postinfectious subgroup. It is not known if these different CVS subgroups exhibit different responses to the varied treatments used for the condition.

General approach

A multidisciplinary approach involving a supervising gastroenterologist, the local primary care giver, as well as nursing support and a psychologist, is useful for management of CVS in children.[70] Similar approaches are likely to be beneficial in adults with CVS. An important component to extend care of individuals with CVS is to involve and educate the EDs as this is where patients with CVS are usually managed during the acute emetic phase. Providing the patient with a letter from the supervising physician describing the syndrome, the patient's prior evaluation, and recommending an appropriate individualized treatment plan often helps facilitate timely, more effective treatment and minimize unnecessary and repeated diagnostic evaluations. Finally, the assurance of a prompt, predictable, effective treatment regimen can reduce the

patient and family anxiety about the care of future emetic episodes.

Frustrations resulting from a relapsing, disruptive illness with frequent ED visits, common misdiagnosis, extensive and redundant testing, mandate psychosocial support for both patients and their families. The CVSA is a non-profit organization that provides a support network and education to patients and families, distributes resources to professionals and supports biomedical research. Cyclic Vomiting Syndrome Association has been helpful to paediatric and adult patients, families and physicians. The CVSA patient database now consists of more adult patients (some self diagnosed) than children. The internet site for CVSA is http://www.cvsaonline.org.

Lifestyle changes

Lifestyle changes may be instituted during the interepisodic phase. Avoidance of excessive emotional excitement, energy-depleted states (sleep deprivation, fasting and illness), triggering foods (e.g. chocolate, cheese, monosodium glutamate and red wine), motion sickness and other identified triggers is helpful (Table 5A). As with migraine headaches, eliminating or stabilizing caffeine intake may be helpful. In some women, episodes can be triggered by menses, so-called catamenial CVS and pharmacological intervention to cease menstruation can be considered. Diabetes needs to be aggressively managed with the goal of glucose control for blood glucose to remain <160 mg dL^{-1}. Episodes of hypoglycaemia must also be avoided as this may also trigger episodes.

Prophylactic therapy

Recommendations for daily prophylactic pharmacotherapy to prevent future emetic episodes in the patient with CVS are dependent on patient age, associated medical and psychological comorbidities, the dosage regimen and the side effect profiles of the medications (Table 5A). Those patients with a higher frequency (e.g. >one episode per month) and greater severity of episodes (e.g. recurrent ER visits and/or

Table 5A Chronic prophylactic treatment for cyclic vomiting syndrome

Lifestyle changes
Avoidance of potential triggers
Migraine headache
Excessive emotional excitement, anxiety, panic
Energy-depleted states (fasting, infections, illness)
Triggering foods (e.g. chocolate, cheese, MSG)
Motion sickness and other identified triggers
Menses: consider oral contraceptive agents
Relaxation routines
Controlling blood sugar in diabetic patients
Medications (prophylactic therapy to prevent subsequent episodes)
Tricyclic antidepressants
Amitriptyline, imipramine, or other tricyclic antidepressant; 10–100 mg day^{-1}
Beta blockers
Propranolol; 80 mg day^{-1} in divided doses
Antihistamines
Diphenhydramine (Benadryl)
Serotonin inhibitor
Cyproheptadine (Periactin) in children
Antianxiety medications
Lorazepam (Ativan) 1 mg dose up to 4 per day
Control comorbid symptoms, illnesses
For abdominal pain, address irritable bowel syndrome: use anticholinergic agents or tramadol for pain
For breakthrough nausea, particularly in the amitriptyline, chlorazepam or scopolamine patch
For gastro-oesophageal reflux symptoms, H2 blockers, proton pump inhibitors
For diabetic patients, maintain glucose at <160 mg dL^{-1} and prevent hypoglycaemia
If menstrual cycles trigger an attack, consider Lupron injection or continuous birth control to block menses
For morbid depression, psychiatry consultation

hospitalizations, frequent absence from school or work, failure to respond to abortive therapy) are most likely to benefit from prophylactic treatment. Medications most often used for prophylaxis include TCA, cyproheptadine and propranolol.

Tricyclic antidepressants are the most commonly employed drug class for the prevention of CVS attacks in adults.[71,72] These agents also play a prophylactic role in migraine, depression, anxiety and the abdominal pain associated with irritable bowel syndrome and presumably act centrally to modulate the vomiting process.[73] Low dose TCAs (25–50 mg day^{-1}) induced complete remission in nearly one of five patients and partial response in over half of affected individuals in one series.[71] At higher TCA doses (e.g. amitriptyline at 1 mg kg^{-1} day^{-1}), 93% of patients in a second series experienced a decreased frequency and severity of attacks while one-quarter achieved full remission.[14] Treated patients reported improvement in anxiety and mood symptoms, as well as prevention of migraine. Based on these data and the personal experience of the authors, amitriptyline is the preferred TCA to treat adults with CVS. A step-up approach is typically advocated for prescription of TCAs beginning with low initial doses (e.g. 10 mg at night) with incremental increases in dose (in some cases to 100 mg daily) to titrate to the desired therapeutic effect. The rationale for this approach is that lower doses may be therapeutic in some cases and may limit side effects that can occur with higher doses. Tricyclic antidepressants may take up to a month to achieve full therapeutic effect following initiation and each dose escalation. More recently, the anticonvulsant agents zonisamide and levetiracetam agents have demonstrated efficacy in adult patients with CVS unresponsive or intolerant of TCAs.[74]

For chronic prophylactic therapy, other considerations may need to be addressed:

1 If amitriptyline dosing cannot be increased due to side effects, TCAs with fewer side effects such as nortriptyline, imipramine or desipramine can be employed.
2 If there is a migraine component to the CVS attacks, the β-adrenoceptor antagonist propranolol or in children the histamine (H_1)/serotonin receptor antagonist cyproheptadine (periactin) can be used or added to the TCA regimen providing bronchial asthma has been excluded.
3 If anxiety is present during or between attacks, benzodiazepines such as lorazepam (1 mg p.o. t.i.d. initially) can be used.
4 Irritable bowel symptoms between acute attacks attributed to the gastrocolonic reflex related to rapid gastric emptying may respond to antispasmodic agents such as dicyclomine.
5 If gastro-oesophageal reflux symptoms are present after acute vomiting relapses, patients may need 1–2 months of a proton pump inhibitor which then can be tapered.
6 Interepisodic nausea may necessitate the use of antiemetic agents such as ondansetron, promethazine, or prochlorperazine.
7 Abdominal pain that does not fully subside between attacks after may require tramadol and non-narcotic analgesics. A very small subset unfortunately may require narcotic use between episodes. Co-management with a pain specialist is recommended for these individuals.
8 For the subset of patients with significant depression, co-management with a psychiatrist may be indicated to select antidepressant therapies with the least likelihood of exacerbating the emetic illness.

Acute abortive treatment during the prodromal phase

A variety of therapies may be administered in some cases during the prodromal phase to abort an oncoming emetic episode (Table 5B). Supportive care is needed for patients not responding to abortive treatment. The treatment approach is largely adapted from clinical experiences in treating CVS in children. There is a paucity of data in both children and adults, and most recommendations are based on medium-sized case series and expert opinion.[75,76]

Table 5B Management during prodromal phase for cyclic vomiting syndrome

Lifestyle changes/relaxation techniques
Decrease stress (lie down in dark, quiet room)
Consider hot bath or hot shower
Anti-emetics
5-HT_3 receptor antagonists: ondansetron, granisetron, palonosetron, dolasetron
Antihistamines: diphenhydramine (Benadryl)
Phenothiazines: promethazine (Phenergan), prochlorperazine (Compazine)
Anxiolytics
Benzodiazepines: lorazepam (Ativan)
Antimigraine
5-HT_{1D} agonist: sumatriptan, zolmitriptan, frovatriptan
Miscellaneous
High carbohydrate liquid ingestion
Consider ibuprofen

Table 5C Treatments during emetic phase for cyclic vomiting syndrome in adults

General	Class	Specific example
Supportive care		Dark, quiet surroundings
Hydration	Intravenous fluids	D_{10}0.45 NS at 1.5 times maintenance
Anti-emetics	5-HT_3 receptor antagonists	Ondansetron
	Phenothiazines with H1, D2, ACh blockade	Promethazine, prochlorperazine
	D_2 receptor antagonists	Metoclopramide, domperidone
	Antihistamines	Diphenhydramine
Anxiolytic	Benzodiazepines	Lorazepam
Analgesics	NSAIDs	Ketorolac i.v./i.m.
	Opioids	Hydromorphone (Dilaudid)
		Fentanyl
Antimigraine	5-$HT_{1B/1D}$ agonist	Sumatriptan
Gastric acid suppressants	Proton pump inhibitors	Omeprazole
	H_2 receptor antagonists	Ranitidine

Early pharmaceutical intervention during the prodromal phase, similar to that employed for migraine, may be effective in some cases. Administration of oral non-steroidal anti-inflammatory drugs and ingestion of caffeinated sweetened beverages are advocated by some experts. Oral or intravenous dextrose also can truncate episodes in some patients if given during the prodromal phase or very early in the emetic episode. The most useful pharmacological abortive approach endorsed by the Pediatric Guidelines Committee of North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) is use of antimigraine $5HT_{1B/1D}$ receptor agonists such as sumatriptan at the earliest sign of an attack.[75] These agents are more often effective in children if there is a positive family history of migraine, if administered early in the prodromal phase or emetic phases, and if the episodes last <24 h. Such drugs can be administered subcutaneously or intranasally and can stop episodes within 30 min to 2 h in about half of the patients. The use of this class of antimigraine drugs is less well studied in adult patients.

Treatment during the vomiting phase

When the prodromal phase has progressed to relentless emesis, evaluation and treatment in an ED or direct admission to the hospital ward is often necessary to relieve suffering and to prevent severe dehydration. The goal during the vomiting phase is prompt treatment to prevent dehydration and terminate the nausea and vomiting. Treatments consist of hydration and anti-emetic, antianxiety and/or analgesic medications (Table 5C).

Intravenous fluid replacement is commonly required to maintain hydration. Retrospective analyses have suggested that 50% of CVS cases respond to intravenous dextrose administration during the acute emetic phase. The efficacy appears greater if higher concentrations of dextrose (e.g. 10% solutions) are administered at 1.5 times the usual rate to reduce the ketosis in the ED. As this treatment is benign, readily available, inexpensive and often efficacious, it is recommended.

Anti-emetic agents can ameliorate the severity of the vomiting episode, but usually do not abort the attack. In children, the phenothiazine anti-emetics (e.g. prochlorperazine) are generally not effective when given alone. However, when given with an antihistamine such as diphenhydramine, symptom relief may be observed in part due to the sedating effect of the latter agent. 5-HT_3 receptor antagonists such as ondansetron may be effective during the acute emetic phase when administered in high doses.[6] Ondansetron is available in oral, sublingual and intravenous forms. All anti-emetic therapies of CVS appear to be more effective when used in conjunction with sedatives.

The greatest relief is often achieved when a deep sleep is induced which renders the patient insensible to their intractable nausea and which also reduces anticipatory anxiety related to the ongoing emetic episode. In adults, sedation is most commonly provided by intravenous administration of a benzodiazepine (e.g. lorazepam). This should be given as quickly a possible when a typical episode commences and the patient presents to the ED setting (1–2 mg every 2 h). It should be continued in the hospital if resolution cannot be achieved in the ED. This approach also lessens the need for narcotics and anti-emetics.

Abdominal pain may be a dominant symptom during the acute emetic episode. In some cases, an intravenous non-steroidal agent such as ketorolac may provide symptom relief. Other patients require narcotic

Table 5D Experimental therapy for cyclic vomiting syndrome in adults

Mitochondrial stabilization	
L-Carnitine	330 mg tablets: 2–3 tablets two to three times daily, up to 3 g day^{-1} > 8 weeks
Co-enzyme Q-10	up to 10 mg kg^{-1} day^{-1} > 8 weeks
Autonomic dysfunction	
α-receptor antagonist	Phentolamine (non-selective)
	Dextromedetomidine (α_2 selective)
Anti-emetic	
NK1 receptor antagonist	Aprepitant (Emend)
Anti-epileptic agents	Zonisamide, levetiracetam

analgesics for pain control. Opiates reduce CRF secretion by the hypothalamus and have both analgesic and anxiolytic effects. Some individuals will respond only to very potent short acting agents such as hydromorphone.

Novel treatments

Pharmacological treatments for CVS are the focus of ongoing research (Table 5D). Some patients with CVS are already using agents purported to improve mitochondrial function. L-Carnitine is an amino acid-like compound whose primary function is to transport long-chain fatty acids into mitochondria for oxidation.[77] Oral L-carnitine has been reported to reduce the frequency of CVS attacks in some cases.[78,79] Co-enzyme Q10, a hydrophobic substance, serves as an electron carrier in the mitochondrial respiratory chain and as an anti-oxidant. Although it has been demonstrated efficacy in migraine headaches, the utility of this agent in CVS has not been confirmed.[80,81] Other pharmaceutical agents under consideration for treatment of CVS include agents that correct possible autonomic defects observed in CVS (e.g. phentolamine[82] as well as anti-emetic agents) directed to novel receptors (e.g. the NK1 receptor antagonist aprepitant).

Future directions

Cyclic vomiting syndrome has been best characterized in children, but evidence has accumulated that a CVS-like illness presents in adults which may be primary or secondary to systemic disease or substance abuse. The current understanding of the clinical spectrum of adult CVS (including a broad agreement on the diagnostic criteria for the disorder), factors involved in its pathogenesis, and therapies which prevent emetic episodes or reduce symptoms once an episode is steadily evolving. To date, information on the syndrome has been provided by small to moderate sized single centre case series amassed by a small number of experts in CVS (Table 6). Further progress in understanding the pathogenesis and improving diagnosis and treatment approaches for CVS will be promoted by the following strategies. Firstly, this consensus document prepared by experts should be disseminated to gastroenterologists and other providers caring for adult patients to enhance awareness and subsequently to more rapidly diagnose the patient with CVS. Secondly, a registry of adults who satisfy the diagnosis of CVS should be established using non-restrictive inclusion criteria to facilitate characterization of the spectrum of clinical presentations. Such a registry could be accessible online and could be maintained by a dedicated group of expert investigators. Information provided by the registry could help provide the basis for the development of consensus diagnostic criteria for adults and the construction of a diagnostic questionnaire. This registry could help define relationships of adult CVS with

Table 6 Cyclic vomiting syndrome in adults: areas where research is needed

- Establish a consensus standardized questionnaire and registry for adults with CVS
  - Validate diagnostic criteria in a well-defined clinical population to further characterize the clinical phenotype and prevalence of gastrointestinal and psychological comorbid conditions
  - Establish the natural history in a prospective fashion
- Increase awareness of CVS in adults
  - Gastroenterologists
  - Emergency room physicians
- Continue and initiate individual studies of pathophysiological mechanisms
  - Mitochondrial DNA dysfunction
  - Corticotropin-releasing factor
  - Autonomic nervous system dysfunction
  - Gastrointestinal motility relationships
  - Role of viral infections and other illnesses as 'triggers'
  - Central nervous system imaging in patients with CVS
    - Before, during and after resolution of episode
    - Before and during treatment with resolution
- Conduct multicentre trials on treatment of CVS in adults
  - Antimigraine therapies
  - Antidepressant therapies – amitriptyline
  - Anticonvulsant medications
  - Mitochondrial stabilizers – co-enzyme Q10, L-carnitine
- Psycho-physiology and management of panic disorder in CVS
- Management of CVS in pregnancy without the use of potentially teratogenic agents

CVS, cyclic vomiting syndrome.

other systemic illnesses and quantify the prevalence of comorbid GI disorders (e.g. irritable bowel syndrome, gall bladder disease and sphincter of Oddi dysfunction) and psychological conditions (e.g. anxiety and mood disorders). The registry also could serve as a source of potential subjects for future research into factors underlying disease development and for placebo-controlled, multicentre treatment trials. Such an approach would confirm or refute the benefits of medication classes such as antimigraine or anticonvulsant agents in controlled trials, the uses of which currently are supported only by anecdotal evidence. Examples of ongoing research elucidating the underlying pathophysiological mechanisms of CVS in adults specifically include investigations of mtDNA mutations and mitochondrial dysfunction, and pilot studies on the role of CRF in symptoms induced in the disorder. Establishment of multicentre treatment trials will be challenging because of the need to generate a substantial research infrastructure, initiate stable interinstitutional cooperative agreements and solicit government or pharmaceutical funding.

SUMMARY

Cyclic vomiting syndrome is a debilitating functional brain–gut disorder that was initially characterized in children, but now is increasingly recognized to occur also in adults. Although the prevalence is unknown, the authors have observed a rapid rise in referrals for adult patients with CVS over the last several years. Although the pathogenesis remains unknown, several promising avenues are being pursued including roles for abnormal central nervous system processing, aberrant CRF production, abnormal gastric emptying suggesting dysautonomia and mitochondrial dysfunction. Based on small case series and expert opinions, TCA appear useful as preventative agents and triptrans are effective in some patients as an abortive agent. Benzodiazepine sedatives can ameliorate symptoms during acute emetic episodes with support from serotonin 5-HT_3 receptor antagonist anti-emetics and NSAIDs or narcotic analgesics. This review might serve as a catalyst to begin collaborative efforts to enhance our understanding of the clinical features and pathophysiology of the disease and to stimulate controlled investigations into novel treatments for this disabling condition.

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