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Cyclic Vomiting Syndrome

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Cyclic vomiting syndrome (CVS) is a chronic functional disorder characterized by episodes of severe nausea and vomiting that alternate with prolonged symptom-free intervals.[1] Symptoms are often triggered by social stress; episodes can occur after the loss of a loved one, job-related stress, during exams, and even on vacations.[2] The etiology of CVS is not known, but several theories have been proposed, including genetic factors in children and marijuana use in adults. Patients also have many associated conditions, including a history of migraine and autonomic dysfunction and high rates of anxiety and depression. While CVS is generally not life threatening, it is associated with significant morbidity. Many patients are often misdiagnosed as having viral gastroenteritis, gastroparesis, or even psychogenic vomiting given the lack of awareness in the medical community.[3] Approximately 20% of patients are subjected to surgical procedures such as cholecystectomies and appendectomies that fail to improve their symptoms. Affected adults also have multiple emergency department visits and hospitalizations for relief of symptoms, which poses a significant economic burden on limited health care resources.[3] Prompt diagnosis, education about the disease, and treatment are essential and can reduce severity and frequency of episodes. This review on CVS will elucidate the epidemiology, historical perspective, clinical features, diagnosis, and available therapy in CVS and also provide a suggested algorithm for workup of recurrent vomiting.

History and Epidemiology

Dr. Samuel Gee first described this syndrome in children in 1882 when he noted a pattern of "fitful vomiting in children."[4] He said, "These cases all seem to be of the same kind, their characteristic being fits of vomiting that recur after intervals of uncertain length. The intervals themselves are free from signs of disease. The vomiting continues for a few hours or days. When it has been severe the patients are left much exhausted." Of interest, Charles Darwin, the noted scientist best known for his work on the theory of evolution, also seemed to have suffered from CVS, which AQ1

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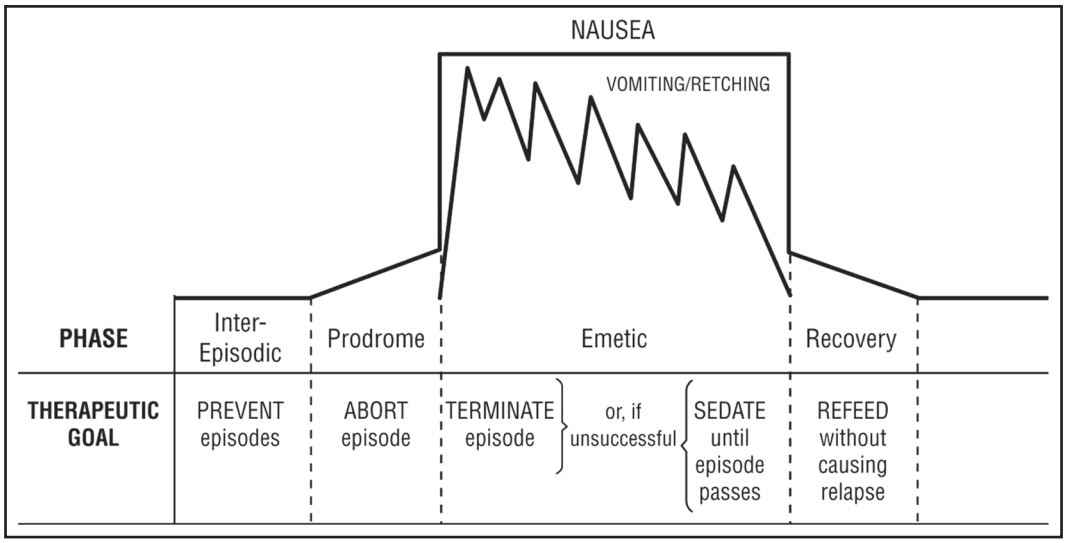

Figure 11-1. Phases of CVS. (From Fleisher DR, Gornowicz B, Adams K, et al. Cyclic vomiting syndrome in 41 adults: the illness, the patients, and problems of management. *BMC Medicine*. 2005; 3:20.) AQ2

spontaneously resolved in his seventies.[5] He also resorted to "water therapy" at the suggestion of his physician to no avail. The clinical description of CVS remains unchanged to the present day and is now characterized by the Rome III criteria.

CVS was initially thought to occur only in children, but it is now clear that CVS occurs in all age groups. It is also more common than originally thought; the estimated prevalence of CVS in children is 0.3% to 2.2%.[6] The incidence of CVS in Ireland (1.3 million children) was 3.15 cases per 100,000 children per year, which was much higher than expected. In a cross-sectional study of school-age children in Scotland, the prevalence was 1.9%.[7]

A similar study in Turkey of 1263 children aged 6 to 17 years showed a similar prevalence of 1.9%. To put this in perspective, the incidence of CVS is comparable to pediatric inflammatory bowel disease.[8] The prevalence in adults is not known, and the absence of a unique diagnostic code for CVS hampers such a determination. In North America, CVS primarily affects Caucasians with a mean age of onset of 35 years in adults and 5 years in children.[9] There does not appear to be a clear gender predilection; some studies have identified a predominance of pediatric CVS in females and adult-onset CVS in males, although reports have been conflicting.[6]

Clinical Features

The hallmark of CVS is a recurrent, stereotypical pattern of symptoms. Patients feel normal in between episodes, and symptoms frequently occur "out of the blue." Many patients report that episodes occur early in the morning, and some have noted a seasonal variation. Cyclic vomiting syndrome can be divided into 4 phases (Figure 11-1): the prodromal phase, the emetic phase, the recovery phase, and the asymptomatic phase, which was described by Fleisher et al.[10]

Phases of Cyclic Vomiting Syndrome

Episodes usually start with the prodromal phase, similar to those seen in migraine patients who will often have a premonition of an impending attack. Symptoms during this phase can include nausea, sweating, epigastric pain, fatigue, weakness, hot and cold flashes, shivering, intense thirst, loss of appetite, burping, lightheadedness, and paresthesias, and patients will describe an

impending sense of doom. Patients also have symptoms of panic during this time and may have difficulty conversing. This phase can last from a few minutes to many hours and even days, and experts often prescribe the use of medications such as triptans, sedatives, and antiemetic agents to abort symptoms although there are no well-designed studies in CVS to support this approach. Patients can be tachycardic and hypertensive during an episode due to the adrenergic drive.

The emetic phase is characterized by unrelenting nausea, retching, and vomiting in addition to the other gastrointestinal (GI) and autonomic symptoms. The frequency of vomiting can vary considerably from once every 2 hours to 20 times an hour or more. The majority of adults with CVS may experience significant abdominal pain, and this should not exclude a diagnosis of CVS. Other symptoms include hot sweats, chills, headache, photosensitivity, sensitivity to sounds, and diarrhea. Patients sometimes report an intense feeling of thirst and will often drink large amounts of water and subsequently vomit, called the "drinking and guzzling behavior." This appears to soothe their symptoms and should not be interpreted as being self-induced or as malingering. Patients often have altered consciousness during episodes that is frequently referred to as a "conscious coma," in which the patient is lethargic, listless, withdrawn, disoriented, and/or difficult to arouse. The patient can also seem very agitated and in a state of panic during an episode. A large proportion of patients report that extremely hot showers or baths alleviate their symptoms, at least temporarily, and this pattern of "compulsive hot water bathing" has been associated with marijuana use. In adults, the emetic phase typically lasts days; in children, it usually lasts hours to a couple of days.[11] Complications include dehydration, electrolyte abnormalities, Mallory-Weiss tears with subsequent GI bleeding, and very rarely esophageal perforation (Boerhaave syndrome) from the intense retching and vomiting.[12] This is followed by the recovery phase when patients return to baseline and are able to tolerate oral intake.

Triggers

Stressors are frequently responsible for triggering CVS episodes in both pediatric and adult populations.[13] Triggers can include infections, diet, lack of sleep, and psychological stressors, both positive and negative. Motion sickness and onset of menses have also been found to be trigger mechanisms.[12]

Subcategories of Cyclic Vomiting Syndrome

Subcategories of CVS have been identified, including CVS plus, catamenial CVS, and Sato's variant of CVS.[14] CVS plus is defined by the presence of at least 2 or more neuromuscular disease manifestations, including cognitive disorders, skeletal myopathy, cranial nerve dysfunction, and seizure disorders. Children with CVS plus are more likely to present at an earlier age and have dysautonomia-related disorders such as migraine, chronic fatigue, and neurovascular dystrophy.[15] Catamenial CVS coincides with a menstrual cycle, and the Sato's variant of CVS was described in children who presented with emesis, hypertension, and depression. With attacks, they were found to have transient hyperglycemia and glycosuria; elevated plasma adrenocorticotropic hormone (ACTH), cortisol, and urinary 17-OHCS excretion; and low plasma osmolality with hyponatremia.[14]

Comorbid Conditions

Adults with CVS have multiple comorbid conditions such as irritable bowel syndrome in 65%, depression and migraine in 55%, syncope in 36%, photophobia in 29%, and other conditions including attention deficit disorder (ADHD), chronic fatigue syndrome, and seizures.[16] In a prospective study of 20 patients with CVS, 90% had impairment of the sympathetic nervous system with sudomotor dysfunction, postural tachycardia, or both.[17] These findings were validated by another study by McCallum et al. The study also confirmed that the majority of patients (57%) had

rapid gastric emptying, which has been associated with autonomic dysfunction.[18] This significant burden of coexistent illness should be borne in mind when treating these patients.

Natural History of Symptoms

In a series of 88 children with CVS, 27% developed migraine headaches with cessation of vomiting, 7% evolved into abdominal migraine, and the majority (65%) became asymptomatic and outgrew their symptoms completely with time. Pediatric patients who develop symptoms later in childhood may have a shorter duration of CVS symptoms.[19]

The natural history of CVS in adults is not known, but approximately 40% of patients lose the typical periodicity and can develop interepisodic nausea and dyspepsia over time, which is referred to as "coalescent CVS" by experts in the field.[10] A careful history and assessment of the patient's symptoms can aid in making an accurate diagnosis, as all patients will have the classic "on-off" pattern at symptom onset.

Pathophysiology

The pathophysiology of CVS is unknown, and both environmental and genetic factors seem to play a role. Pedigree analysis by Boles et al in 80 subjects (mostly children) with CVS revealed a clustering of various functional conditions such as migraine, depression, irritable bowel, and hypothyroidism in over 50% of matrilineal relatives vs. patrilineal relatives. Subsequent studies in children sequencing the mitochondrial genome in Haplogroup H individuals by the same author revealed a significant association between CVS and two mitochondrial DNA single-nucleotide polymorphisms (mt DNA SNPs) 16519 T and 3010A. The presence of both these SNPs was associated with 17-fold increased odds of having CVS. A similar study was then performed in children and adults with CVS, but adults with CVS did not have the mitochondrial SNPs of interest. The authors concluded that CVS might be biologically different based on onset of symptoms. However, the same study also revealed that adults with CVS had high Karolinska Scales of Personality (KSP) scores, which are both sensitive and specific for mitochondrial dysfunction, findings not reconciled by their study results. One possible explanation for this may be the presence of yet unidentified mitochondrial DNA polymorphisms. With the availability of next-generation sequencing, future studies examining the entire mitochondrial and nuclear genome will shed light on this important question of whether mitochondrial DNA polymorphisms contribute to symptoms of CVS.

Emerging research also points to brain-gut interactions as a possible mechanism. CVS is often triggered by emotional stress, suggesting a central mechanism causing symptoms. Preliminary functional magnetic resonance imaging (MRI) studies of patients have shown significant differences in functional connectivity of the nausea network between CVS patients and healthy controls following emotional stress.[20] That stress plays a major role is also supported by recent data showing an increase in salivary cortisol levels during a CVS episode versus the asymptomatic/well phase.[21] Median salivary cortisol levels were also significantly higher during an episode compared to the well phase, with no differences between controls and the well phase in patients.[21]

There is also a considerable amount of interest in the role of marijuana in patients with this condition. A large proportion of CVS patients (approximately 40%) use marijuana for CVS symptoms. A recent survey of 437 patients who used marijuana reported improvement in nausea, vomiting, appetite, general well-being, and stress levels.[22] However, a retrospective study of 98 patients with prior marijuana use was associated with cyclic vomiting. Specific data on marijuana use were available only in 37 patients. Of this subset of patients, chronic daily marijuana use was associated with the "compulsive hot water bathing pattern." Follow-up data of 1 to 3 months were available only in 10 patients.[23] These findings need to be reconciled with the antiemetic

Table 11-1
Rome III Criteria for the Diagnosis of Cyclic Vomiting Syndrome in Adults

1. Stereotypical episodes of vomiting regarding onset (acute) and duration (less than 1 week)
2. Three of more discrete episodes in prior year
3. Absence of nausea and vomiting between episodes
4. No metabolic, gastrointestinal or CNS structural or biochemical disorders
* Must have for at least 3 months with onset at least 6 months previous

effects of cannabinoid agonists in both animal models and use of marinol in humans. The dose of tetrahydrocannabinol (THC) and the exact mechanism of action of phytocannabinoids in nausea and vomiting need to be elucidated in future studies.

The endocannabinoid system consists of 2 endogenous ligands, N-arachidonylethanolamine and 2-arachidonoylglycerol (2-AG); 2 G-protein-coupled cannabinoid receptors (CB1 and CB2); and related synthetic and degradation enzymes. The endocannabinoid system has an important role in modulation of stress as well as nausea and vomiting.[24] Cannabinoid agonists and synthetic delta-9-THC such as nabilone and dronabinol have been used as antiemetics in the past.[25] In a pilot study of CVS, anadamide and 3 closely related compounds called N-acylethanolamines (NAEs), N-oleoylethanolamine (OEA), and N-palmitoylethanolamine (PEA) were significantly increased during an episode vs. the well phase. N-acylethanolamine concentrations were not different between patients in the well phase and controls.[21] Future studies exploring the role of the endocannabinoid system in nausea and vomiting are warranted.

Diagnosis

Currently, the diagnosis of CVS is based on clinical criteria. There is no specific test or biomarker that can diagnose it. A cyclic pattern of vomiting is key in the diagnosis. The Rome III working group has developed criteria for the diagnosis of CVS in adults (Table 11-1).[14] The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guidelines for the diagnosis of CVS in children were formulated, as the Rome criteria were not appropriate in children. The NASPHAGN guidelines also emphasize a stereotypical pattern and asymptomatic interepisodic period, but they also define the episodes more specifically (Table 11-2).[26] While Rome III criteria are used in clinical practice, their diagnostic accuracy remains to be proven. For instance, the criteria specify that episodes should last less than a week when in fact patients can sometimes have much longer episodes based on experience. This underscores the need for further research into the mechanism of CVS and development of better diagnostic tools.

Most patients with CVS undergo extensive investigations for their symptoms, and the optimal workup for patients has not been evaluated. It is the practice of most experts to perform at least an upper endoscopy and a small bowel follow-through/computed tomography (CT) scan to exclude gastric and small bowel pathology that can mimic CVS. Algorithm for workup of episodic vomiting is depicted in Figure 11-2. If patients have underlying diabetes mellitus, a gastric emptying study can be useful, although the pattern of vomiting differs in these patients. NASPGHAN

Table 11-2
NASPGHAN Criteria for the Diagnosis of Cyclic Vomiting Syndrome in Children

1. At least 5 episodes, or a minimum of 3 over a 6-month period
2. Episodic attacks of intense nausea and vomiting that lasts 1 hour to 10 days, occurring at least 1 week apart
3. Stereotypical pattern and symptoms in the individual patient
4. Vomiting during episodes occurs at least 4 times an hour for at least 1 hour
5. A return to baseline health during episodes
6. Not attributed to another disorder

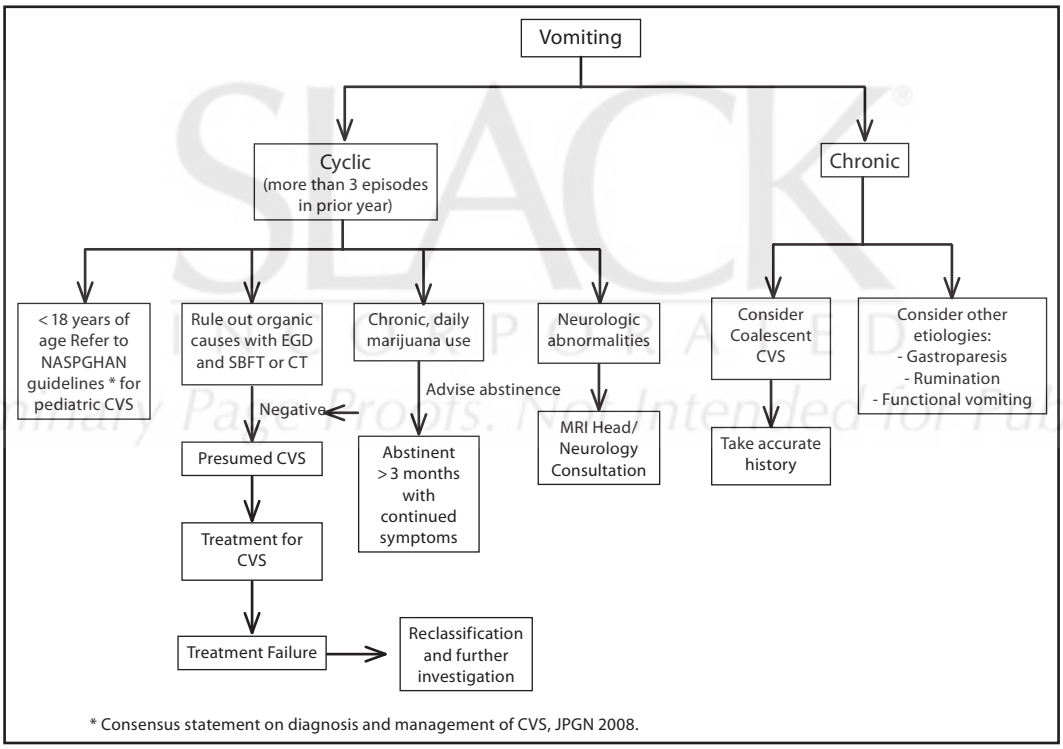

Figure 11-2. Diagnostic algorithm for CVS.

guidelines recommend that children with cyclic vomiting be evaluated for a possible metabolic or neurological disorder if any of the following conditions are met: presentation at less than 2 years of age, vomiting episodes associated with intercurrent illnesses, prior fasting or increased protein intake, and any neurological findings such as ataxia, dystonia, gait disturbance, mental retardation, seizure disorders, or acute encephalopathy.[26]

Patients with neurological disorders or focal neurological signs may need further evaluation with an MRI of the head to exclude structural abnormalities such as intracerebral tumors, hydrocephalus, Chiari malformation, or a subdural hematoma. Patients with CVS can also present

with other intercurrent illnesses such as appendicitis or biliary disorders and must be evaluated carefully upon presentation to ensure that the episode is consistent with their usual CVS flare. If there is clinical suspicion for any other intra-abdominal emergency, workup should be pursued as indicated.

Treatment

A multidisciplinary approach based on a biopsychosocial model is imperative to the successful treatment of a patient with CVS. In addition to pharmacotherapy, adequate reassurance and addressing stressors that trigger episodes are crucial. Treatment of CVS can be divided into 3 categories: 1) prophylactic, 2) abortive, and 3) supportive (Table 11-3).

Prophylactic treatment is typically initiated during the interepisodic well phase. It can include lifestyle modifications aimed at avoidance of triggers, including sleep deprivation, stress, and certain foods. Prophylactic therapy should be considered in patients with severe and frequent symptoms. Tricyclic antidepressants (TCAs) are first-line therapy, although the mechanism of action is unknown. In an open-label study of 41 patients, amitriptyline resulted in an overall subjective improvement in 80% of patients. A prospective open-label study of TCAs in CVS found that 87% of CVS patients responded to therapy with a significant reduction in the number of emergency department visits and hospitalizations over 2 years.[27] Nonresponders were more likely to have a history of migraine headaches, coexisting psychological disorders, chronic marijuana use, and opiate use.[28] In a retrospective review of 101 adult patients with CVS, 86% were found to respond to a prophylactic medication regimen of amitriptyline and/or topiramate and mitochondrial supplements. Nonresponse was associated with noncompliance, chronic marijuana use, coalescence of symptoms, chronic opiate use, severity of disease, and disability, but only noncompliance was a significant factor on multivariate analysis. Doses of TCAs that are effective in CVS are typically higher than those used for other functional GI disorders, and 1mg/kg in children and 80 to 100 mg/daily in adults have been effective. Medications are typically administered at night, as daytime sedation is a frequent side effect. Monitoring of the QT interval is also suggested in these patients given the small risk of cardiac arrhythmias. Other medications shown to be effective include anticonvulsants such as Zonegran (zonisamide), Keppra (levetiracetam), and topiramate.[29] Mitochondrial treatment such as coenzyme Q10,[30] riboflavin, and carnitine[31] was beneficial in a small retrospective study. Future double-blind, therapeutic, placebo-controlled trials are warranted in CVS to determine optimal therapy.

The antimigraine medications called triptans have been found to be effective in aborting CVS attacks. In a study of adult patients with both adult- and pediatric-onset CVS, 89% responded to intranasal administration of triptans.[32] During an episode, supportive treatment may include sedation, hydration, antiemetics, and analgesics. Sedation with lorazepam and/or diphenhydramine is frequently used. Analgesics with opioids may be necessary to control abdominal pain if present during the attack. Intravenous (IV) fluids are used to prevent dehydration. Anecdotally, IV fluids containing 10% dextrose have been thought to be more effective, although prospective data are lacking. Experts also recommend abstinence from chronic marijuana use, as this seems to be associated with nonresponse to treatment. However, the role of marijuana in CVS needs further study given that cannabinoid agonists are antiemetic, but chronic heavy marijuana appears to perpetuate vomiting episodes. A subset of CVS frequently utilizes the emergency department, and emergency medicine physicians play a critical role in their care. Appropriate referral and early recognition of the pattern of symptoms may prevent future episodes.[3]

Table 11-3
Medications Used in the Treatment of Cyclic Vomiting Syndrome

MEDICATION	DOSAGE	SIDE EFFECTS	SPECIAL CONSIDERATIONS
Prophylactic Therapies			
Tricyclic Antidepressants			
Amitriptyline/ Nortriptyline	80 to 100 mg/ daily	Drowsiness, weight gain	Regular monitoring of QT interval
Supplements			
Coenzyme Q10	200 mg bid	Elevated liver function tests	
L-carnitine	100/mg/kg/day divided bid	Fishy odor	
Anticonvulsants			
Topiramate	100 mg bid	Acidosis, nephrolithiasis	Basic metabolic panel every 6 months
Zonisamide	400 mg daily	Somnolence, muscle weakness	
Antihistamine			
Cyproheptadine	0.25 to 0.5mg/kg/ day tid or qhs	Drowsiness, dry mouth, weight gain	Use as first line in children < 5 years
Abortive Therapies			
Triptans			
Sumatriptan	Nasal spray		Contraindicated in CAD
Zolmitriptan	Nasal spray		Contraindicated in CAD
Antiemetics			
Ondansetron	8 mg every 6 hours prn	QT prolongation	Regular monitoring of QT interval
Promethazine	25 mg every 6 hours prn	Drowsiness, dry mouth	
Aprepitant	1 kit (125 mg/80 mg/80 mg)	Fatigue	

CAD: coronary artery disease.

* All of the medications are off-label uses.

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Conclusion

CVS is a chronic functional disorder associated with stereotypic episodes of nausea, vomiting, and abdominal pain with a return to normalcy once an episode has been terminated. This usually afflicts children and young adults and may be more common than once thought. There is unfortunately a significant delay in diagnosis, with patients being subjected to extensive investigations and even unnecessary surgery. Prompt diagnosis and treatment with TCAs for prophylaxis are recommended. Other medications such as coenzyme Q10, carnitine, and riboflavin targeted at mitochondrial function may also be used as preventive therapy. Abortive medications such as nasal triptans and antiemetics may be used in the prodromal phase. Patients are also advised about marijuana cessation, as marijuana use appears to worsen symptoms. Other comorbid conditions such as anxiety, depression, and autonomic dysfunction need to be addressed. Cyclic vomiting syndrome takes a significant toll on both patients and families, and about 20% of patients are disabled. CVS sufferers and their families may avail of services offered by voluntary, nonprofit organizations such as the Cyclic Vomiting Syndrome Association (CVSA) and the International Foundation for Functional GI Disorders (IFFGD), which provide support for patients and families. Studies that explore the pathogenesis of this disorder should provide an avenue for the development of better treatment in the future.

Key Points

- CVS is a chronic functional disorder of unknown etiology and is characterized by stereotypic episodes of nausea and vomiting.
- CVS occurs in both children and adults and affects mostly Caucasians in North America.
- Diagnosis is made with Rome III criteria in adults and NASPGHAN criteria in children.
- CVS is associated with high rates of health care utilization and poor quality of life.
- Use of TCAs as prophylactic agents in adults and cyproheptadine in children <5 years of age is effective in controlling symptoms.

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