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Cyclic Vomiting Syndrome: What a Gastroenterologist Needs to Know

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BACKGROUND: CVS (cyclic vomiting syndrome) is a functional disorder that may occur in any age group of patients. In the past the disorder was considered to be fairly uncommon of unknown etiology. Treatment has generally been based on anecdotal reports.

METHODS: Literature review was performed based on internet/Medline search as of April 2006.

RESULTS: CVS is much more common than previously thought, especially in adults and is commonly associated with migraine headaches and sharing many of its characteristic features. Genetic association with mitochondrial DNA has been recognized with CVS. Prompt diagnosis is essential in order to prevent the significant morbidity associated with CVS. It is mandatory to rule out certain life-threatening disorders that can mimic CVS. Treatment options are based on the particular phase of the syndrome in which a patient is in and carried out in a systematic manner.

CONCLUSION: Expert consensus is that CVS is a distinct disorder and is a part of the migraine spectrum (migraine headaches, CVS, and abdominal migraines). Once patients are properly diagnosed, treatment is highly effective. Because of renewed interest in CVS since the 1990's, many more patients in all age groups are being recognized who suffer from this disabling disorder. An increase in basic science and clinical research in CVS will hopefully lead to better patient outcomes.

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INTRODUCTION

Cyclic vomiting syndrome (CVS) is an episodic disorder of nausea and vomiting that was first described in children, but may affect patients of any age. The cyclic vomiting pattern consists of recurrent episodes of high intensity nausea and vomiting lasting hours or days, separated by intervals free of symptoms (1) (Table 1). The pattern has many etiologies. The syndrome is a functional disorder considered to be a manifestation of migraine diathesis (2, 3). Patients typically present with six to twelve stereotypic episodes of nausea and vomiting per year that vary in duration and frequently go undiagnosed for years (4). The diagnosis of CVS is primarily based on history and clinical presentation. Treatment focuses on symptom management and prompt measures aimed at aborting or terminating episodes. Antimigraine medications have been effectively used for prophylaxis in many patients.

This review is based on the information available as of April 2006. We searched MEDLINE, UptodateOnline, and CVSAonline.org for "cyclic vomiting," "CVS," "cyclic vomiting syndrome," "abdominal migraine," "chronic vomiting," and "CVS and migraine."

HISTORICAL PERSPECTIVE

CVS was first described by Dr. W. Heberden (5) in the French literature in 1806 and later by Dr. Samuel Gee (6) in the English literature in 1882. Many of Dr. Gee's observations continue to be used as diagnostic criteria for this disorder. Existing pathophysiologic evidence points towards CVS as a brain-gut disorder involving neuroendocrine pathways in genetically predisposed individuals (7–9). Since Dr. Gee's initial description, at least six large series of CVS patients have been published. In the 1990s, renewed interest in CVS led to international conferences in 1994 and 1998.

DEMOGRAPHICS AND EPIDEMIOLOGY

CVS has been described in all races and ethnicities (10), although whites appear to be effected to a greater degree than other races. The prevalence of CVS is not known. Li and Misiewicz (10) estimated it to be 0.04% in children of central Ohio. In contrast, a population-based study performed in Aberdeen, Scotland (11) indicated a prevalence of 1.9%. The discrepancy in these two studies may be due to the fact that, in the Ohio study, not all patients with CVS may have been referred to specialty centers and community physicians may have managed patients with milder forms of the disease. In the Scottish study, most patients were diagnosed by survey questionnaire and follow-up history, without detailed diagnostic evaluations to rule out organic etiologies for vomiting. Therefore, the actual incidence in the Scottish study might

Table 1. Rome III Diagnostic Criteria for CVS

At least 3 months, with onset at least 6 months previously of
1. Stereotypical episodes of vomiting regarding onset (acute) and duration (<1 wk).
2. Three or more discrete episodes in the prior year.
3. Absence of nausea and vomiting in between the episodes.
4. There are no metabolic, gastrointestinal, or central nervous system structural or biochemical disorders.
5. Supportive criteria: personal or family history of migraine headaches.

have been lower and it is likely that the true prevalence of CVS is somewhere between these two values.

CVS occurs in all age groups. Children as young as 6 months and adults as old as 73 yr have been described as having CVS (10, 12). The median age at onset of symptoms ranges from 5.2 to 6.9 yr (1, 13). Recent evidence suggests that CVS is much more common in adults than previously thought (13, 14). Fleisher *et al*. recently described 41 adults with CVS. There is a slight female predominance with the ratio being 55:45 (13).

SYMPTOMS AND ASSOCIATED FEATURES

CVS has four phases: interepisodic, prodromal, vomiting, and recovery. Recognition of this phasic pattern helps in making the diagnosis and in management. The interepisodic phase is more or less symptom free. The patient senses the approach of an episode during the prodromal phase, but is still able to take and retain oral medications. The vomiting phase is characterized by intense, persistent nausea, vomiting, retching, and other symptoms. The recovery phase begins as soon as nausea remits and ends when the patient has recovered appetite, strength, and body weight lost during the vomiting phase.

The severity of CVS is mild if the illness doesn't interfere with work or school, moderate if attendance at work or school is in jeopardy, and severe if the patient is disabled and sick more than well.

Prodromal symptoms consist of nausea, lethargy, anorexia, and pallor. A migraine-like visual aura is rare. The nausea, vomiting, retching, and other symptoms of the vomiting phase are overwhelming and completely incapacitating. Their mean duration is 41 h (median, 24 h). The maximum frequency of vomiting may be more than 10 times per hour (13). The total number of emeses amounts to 11 (median) and 22 (mean) emeses (1). Forceful vomiting and retching often cause hematemesis due to prolapse gastropathy or Mallory-Weiss tears (1, 13, 15–17). Peptic esophagitis and hemorrhagic lesions of the gastric mucosa are typical endoscopic findings that result from, rather than cause, vomiting episodes. Abdominal pain has been reported in 58% of adults during the prodromal and vomiting phases of attacks (13). Signs and symptoms of an intense stress response are common, including increased heart rate and blood pressure, drenching diaphoresis, minor loose stooling, low-grade fever, neutrophilia without bandemia, and inability to think clearly to give an accurate history. Many patients have behaviors during episodes that may puzzle or mislead caregivers, but remit promptly during the recovery phase. Patients are characteristically intolerant to being kept waiting for relief; individuals who are normally pleasant and cooperative may become irritable, verbally abusive, and demanding (13). Many patients take prolonged hot baths or showers during episodes and report that contact with hot water lessens their nausea, an effect that ceases as soon as they are out of water (13, 18). Some patients crave water to drink. Others not only drink large amounts, but also make themselves vomit after doing so. This "guzzle-and-vomit" behavior is done for the purposes of diluting the irritants in their vomitus and to achieve the momentary lessening of nausea that follows rapid emptying of the stomach (13). Abdominal pain and leukocytosis have prompted unnecessary cholecystectomies and other abdominal surgeries (13).

Anorexia (74%), lethargy (87%), pallor, increased salivation, and social withdrawal are dysautonomic accompaniments of severe nausea (1, 15). Headache (40%), photophobia (32%), and phonophobia (28%) may occur and cause patients to seek a quiet and dark environment.

Frequency and Temporal Relationships of CVS Episodes

The frequency of CVS episodes ranges from 1 to 70 episodes per year with an average of 12 episodes a year (1, 15). Patients with uncomplicated CVS are asymptomatic between episodes; attacks have an "on-off" pattern (16). About half of the patients have fairly regular recurrences that are more or less predictable. Each episode tends to be stereotypical and characteristic for each patient in terms of time of onset, intensity, episode duration, and associated symptoms. Vomiting typically begins either during the night, waking the patient from sleep, or occurs in the morning; nevertheless some patient have variable times of onset (13) (Table 2).

Trigger Mechanisms for CVS

Most (68–80%) CVS attacks have associated trigger mechanisms. These include infection (41%, often chronic sinusitis and other upper respiratory infections), psychological stress (34%, both positive [birthdays and holidays] and negative [parental or interpersonal conflict]), physical stress (18%, often heavy exercise), inadequate sleep, diet (26%, especially chocolate, cheese, monosodium glutamate), motion sickness (9%), and onset of menses (named catamenial CVS and found in up to 13% of postmenarchal girls) (4, 12, 13). Li and Hayes reported eight post-menarchal girls who had episodes only with the onset of their menses (19). Attacks tend to occur less commonly during the summer months (Table 3).

Psychological Factors Associated With CVS

Patients with CVS have been described as having similar personality traits, although this has not been studied prospectively (13). Many CVS patients have been described as being

Table 2. Associated Diseases

Diseases	Prevalence in CVS Patients	Prevalence in General Population (Wherever Applicable)
Migraine	11–40%	9–20%
Irritable bowel syndrome (IBS)	67%	10–20%
Headache	52%	Unavailable
Motion sickness	46%	*
Seizure disorder	5.6%	0.5–1%
FH/GP of IBS	62% (FH)	14% (GP)†
FH/GP of headache	58% (FH)	16% (GP)†
FH/GP of CVS	3% (FH)	0.4–2% (GP)

*Motion sickness is inducible in almost all adults depending upon the specific preponderance of the individual.
†Data from NWHIC (National Women's Health Information Center).
Ref: (1, 12, 16, 15, 19).

competitive, perfectionist, high achieving, aggressive, strong willed, moralistic, and/or enthusiastic (20). However, these characterizations of CVS patients' personalities may be related to a referral bias as well as self-selection of which CVS patients seek medical attention.

Anxiety is surprisingly prevalent in adult patients (13). It seems to have three sources: (a) the burden of illness, including physical suffering and the economic and marital stress caused by it; (b) anticipatory anxiety for the episode-to-come (21); and (c) anxiety originating in psychological trauma experienced during childhood or prior to the onset of CVS (13).

It is crucially important for the gastroenterologist to attend to the patient's emotional state because mounting frustration and anticipatory anxiety increase the level of autonomic hyperactivity between attacks to an extent approaching the dysautonomic state during the prodromal phase. In such cases, patients may develop almost constant dyspeptic nausea (13), which worsens after food intake and causes them to loose weight. Sleep becomes poor. Their attendance at work or school falls off. If they cannot learn the diagnosis of their illness or find a physician who is knowledgeable and promptly responsive to their needs, they typically become fearful that they have an illness no one can diagnose or treat. This leads to the deterioration in the course of CVS characterized by coalescence of attacks, *i.e.*, increasingly frequent episodes and more anxiety and dyspeptic nausea between episodes. Complete coalescence causes the patient to be sick for weeks or months at a time and sick more than well. In a series of 41 adults with CVS, 32% had coalescence of episodes to the extent that they were completely disabled and required financial support (13).

Table 3. Precipitating Factors for CVS

1. Stress
   a. Physical: infections, sleep deprivation, exercise, trauma
   b. Emotional: holidays, birthdays, family vacations, festivals, school camps, examinations, familial conflicts, anxiety
2. Menstruation
3. Pregnancy
4. Food allergies

Ref: (1, 10, 13, 15).

ASSOCIATIONS BETWEEN MIGRAINE, ABDOMINAL MIGRAINE, AND CVS

Migraine headache**,** abdominal migraine, and CVS all seem to be manifestations of migraine diathesis (3). Each is a functional, episodic disorder with attacks separated by symptom-free intervals. Patients with any of these disorders may experience headache, abdominal pain, nausea, and other symptoms of migraine during their respective attacks. However, the semantic distinction of these three syndromes is based on their predominant symptoms: headache predominates in migraine; intense, sustained, midline abdominal pain predominates in abdominal migraine; and nausea and vomiting predominate in CVS.

Additionally Wang *et al*. (27) showed similar genetic homoplasmic sequence variants in mitochondrial DNA of patients with CVS and patients with migraine (without associated aura) in comparison to patients with migraine (with associated aura). Of note, the majority of childhood CVS patients progress to migraine without aura (see the prognosis section below).

Key characteristics and comparisons of CVS, abdominal migraine, and migraine headache are summarized in Table 4.

Similarities Between CVS and Abdominal Migraine

In both CVS and abdominal migraine, the incidence of migraine headaches experienced by patients' mothers was noted to be twice that of fathers, another possible indication of a mitochondrial inheritance pattern (1, 15). Patients with both CVS and abdominal migraines have been reported to benefit from migraine prophylaxis. A combined CNS electrophysiological evaluation (as a visually provoked b-activity, high-frequency photic response, event-related potential measure), performed on both patients with CVS and abdominal migraine, showed these measures to be very similar to migraines and significantly different from controls (28). Autonomic testing in migraine patients and CVS patients showed an abnormal predominance of adrenergic over cholinergic function in both groups compared to controls (29).

ETIOPATHOLOGY

Proposed mechanisms by which CVS occurs are based primarily on clinical observations of CVS and related conditions, including anecdotal reports (13). Animal models and experimental designs have not been developed for CVS *per se* but rather have been adapted from presumably related disorders such as migraine headaches. In addition to the recent work on mitochondrial gene mutations, other commonly proposed etiologies for CVS include hormonal dysfunction, gastrointestinal dysrhythmias, autonomic dysfunction, food

Table 4. CVS, Abdominal Migraine, and Migraine

Features	CVS	Abdominal Migraine	Migraine Headache
Age at onset	3.7–6.9 yr	7.1 yr	NA
Female : male	3:1	Female>male	3:1
Duration of episodes	1 h–3 days	NA	4 h–3days
Frequency of episodes	Q2weeks–Q3 months	NA	Daily–months
Family history of migraine	40–82%	65%	62%
Prevalence	0.4–1.9%	1.7–2.7%	5–20%
Vomiting	100%	30–70%	40–70%
Abdominal pain	5–80%	100%	10–55%
Headache	35–60%	30–50%	100%

NA = not available.
*Ref: (1, 2, 10, 13, 15, 19, 53).

allergy, and ion channelopathies. In children a number of other disorders have been described as presenting with symptoms identical to CVS, including ureteropelvic obstruction (15).

Endocrine Factors

According to Tache's corticotropin-releasing-factor hypothesis (7), physical or psychological stress releases corticotropin releasing factor (CRF) from the hypothalamus. Two of the many effects of CRF are activation of the locus ceruleus, which increases adrenergic tone, and stimulation of inhibitory motor nerves in the dorsal motor nucleus of the vagus, which inhibits gastric motor activity, a concomitant event, if not the cause, of nausea. The classic function of CRF is stimulation of the anterior pituitary to secrete ACTH, thereby activating the hypophyseal-pituitary-adrenal axis (HPA) and the stress response. Basal secretion of CRF has a diurnal rhythm with increasing secretion beginning at 1 AM, reaching its peak at 6 AM. This may account for the predominance of night and morning times of onset of CVS episodes. Sato and Wolfe have shown that ACTH, cortisol, and catecholamine levels are elevated just prior to vomiting episodes in patients with CVS (7, 8, 30). CRF antagonists have been shown to prevent gastric ileus in postoperative patients in an experimental setting and trunchal vagotomy in experimental animals prevents the gastric inhibitory effects of CRF (7).

Gastrointestinal Motility Disorders

Gastrointestinal motility dysfunction is postulated as a possible etiology in CVS. Abell *et al*. have shown that gastrointestinal dysmotility (hypermotility, hypomotility, or dysrhythmia) involving either the stomach or the small bowel is present even during asymptomatic periods in CVS patients (14). Also, the number of emeses in children with CVS has been reported to decrease by administration of prokinetic agents (31).

Similarly, in migraine patients Boyle *et al*. (32) showed that rates of delay in gastric emptying were significantly correlated with the severity of the migraine attacks. Aurora *et al*. (33) recently published a more direct study in a small group of patients with migraine and compared the patients' gastric emptying with normal controls. They concluded that migraine patients have baseline delayed ictal and interictal gastric emptying with a greater delay in emptying occurring in the interictal phase.

However, contrary to all of the above, a prospective comparative study done at Mayo Clinic, Rochester showed that asymptomatic CVS patients have rapid early-phase (1 and 2 h) gastric emptying and are more likely to have accelerated phase two emptying in comparison to normal controls (34).

The presence of gastric emptying abnormalities in both CVS and migraine emphasizes possible similarities in etiopathogenesis responsible for both disorders. However, it cannot be determined, from the current gastric emptying data, whether underlying gastrointestinal motility disorders are the cause of some episodes of CVS or if CVS results from central nervous system dysfunction that affects the gastrointestinal tract.

Autonomic Nervous System

Autonomic dysfunction has been hypothesized to be a cause of CVS. Rashed *et al*. evaluated adrenergic function measures in CVS and migraine patients and compared them to normal controls and chronic vomiting patients (29, 35). A low and impaired postural adjustment ratio (a sympathetic measure) was seen in CVS and migraine patients in contrast with adult control and adult and pediatric chronic vomiting patients (35).

Welch *et al*. recently evaluated the periaqueductal gray area in the fourth ventricle (which regulates the autonomic nervous system [ANS]) in migraine patients using 31P-NMR spectroscopy (36, 37), which showed this region undergoes progressive oxidative injury that in turn leads to a self-sustaining paroxysmal dysautonomia.

However, it is unclear in these patients whether primary ANS abnormality results in CVS and migraine or if another disorder leads to an ANS abnormality in combination with either CVS or migraine.

Genetic Associations

Most cases of CVS have been described as sporadic, but family history may be an important factor. In Fleisher and Matar's series (15), only 3 of 71 patients had a parent with CVS. Several families, however, have been described with multiple members involved (22–24). In these familial cases of CVS, the mode of inheritance is predominantly matrilineal.

Table 5. Differential Diagnosis

1. Gastrointestinal disorders (nonsurgical): peptic ulcer disease, hepatitis, pancreatitis with or without pseudocyst, motility disorders, inflammatory bowel disease, infections (giardiasis, gastrospirillium, entamoeba coli, blastocystis hominis, pinworms).
2. Gastrointestinal disorders (surgical): pancreatic pseudocyst, recurrent subacute appendicitis, bowel obstruction, intermittent duodenal intussusception, duodenal web/atresia/diverticulum, adhesions, choledochal cyst, cholelithiasis/gallbladder dyskinesia, gastrointestinal malignancies.
3. Urologic/renal/gynecologic disorders: urolithiasis, reteropelvic junction obstruction, ovarian cyst, pregnancy, premenstrual syndrome.
4. Neurological disorders: hydrocephalus/slit ventricle syndrome, brain tumors, budd chiari malformations, epilepsy, subdural hematomas or effusions, familial dysautonomia.
5. Endocrinologic disorders: diabetes mellitus, adrenal insufficiency, pheochromocytoma.
6. Miscellaneous disorders: abdominal migraines/epilepsy, hypothalamic surge, pulmonary (asthma), ENT (chronic sinusitis, benign positional vertigo), psychiatric (anxiety, depression, secondary gain, munchansen-by-proxy).

Ref: (42–51).

This supports the Boles' hypothesis that defects in mitochondrial energy production due to mutations may predispose the onset of episodes of vomiting during periods of heightened demands for energy; for example, stress or excitement (9, 22–27), patients who may be well compensated for usual daily demands. Because the functional integrity of the gastrointestinal tract involves a great deal of interplay between smooth muscle and nervous tissues, gastrointestinal symptoms are often prominent in mitochondrial DNA disorders (26, 27).

Although universal genetic associations of CVS are yet to be identified, case studies of patients and/or families have shown an A3243G mitochondrial DNA mutation along with several other less well-characterized mitochondrial DNA mutations exhibiting vomiting as a common feature (24, 25).

Allergy

Food allergy has been suggested as a possible etiology of CVS. Lucarelli *et al*. evaluated eight children with CVS (38). None of these children had a history of allergic reactions to food. However, most of these children had a positive skin prick test and the specific IgE present for various foods, including cow's milk proteins, soy, and egg white. Elimination of the offending foods from diet led to significant clinical improvement in their CVS symptoms.

Mitochondrial Enzymopathies

Renewed interest in mitochondrial enzymopathies and CVS (23–26, 39, 40) suggested that energy supply and demand might not be met under certain circumstances in predisposed individuals. This energy deficit can alter voltage-gated membrane channels for calcium, magnesium, and other ions. Some patients may have genetic mutations of various ion channels. Perturbations in delicate cellular electrochemical gradients can result in depolarization and hyperexcitability of neurons that in turn could lead to any of the above-mentioned neuroendocrine phenomena.

Miscellaneous Causes

CVS has also been associated with chronic marijuana use (as evident by multiple case reports of CVS in chronic marijuana abusers in Australia); however, it is unclear if this is the cause of CVS *versus* over self-medication by the patients for the relief of the nausea and vomiting. Although a well-done clinical follow-up concluded that *Cannabis* abuse predated the onset of cyclic vomiting and was essentially the cause of the illness (18).

DIFFERENTIAL DIAGNOSIS

A patient can present with vomiting of acute (less than 1 wk), subacute (1 wk to 3 months), or chronic (longer then 3 months) duration (Table 5).

For patients with an acute onset of vomiting, the physician must first consider severe or even life-threatening disorders including many of the anatomic disorders described in Table 4. These possible lesions require prompt recognition and the appropriate surgical therapy.

Some causes of vomiting are not severe or immediately life threatening but can lead to significant morbidity or even mortality if the diagnosis is delayed. These include neurological disorders (*e.g.*, brain tumors or hydrocephalus) or structural gastrointestinal disorders (such as peptic ulcer disease or malrotation of the gut with volvulus).

Many other disorders listed in Table 4 may present with vomiting that is neither severe nor immediately life threatening; these occur rarely and are often diagnosed after an extensive and detailed evaluation.

DIAGNOSTIC EVALUATION

The diagnosis of CVS requires that other known and treatable disorders be excluded. When a patient presents with acute vomiting, severe disorders can usually be excluded by history, physical examination, and basic laboratory studies (such as a complete blood count and a complete metabolic panel including liver function tests, amylase, and lipase, a urinalysis, a pregnancy test, and an upper GI series/small bowel follow through).

Abdominal ultrasound of the liver, gall bladder, pancreas, kidneys, and adrenals may help in evaluation of possible gallstones, pancreatitis, and ureteropelvic junction obstruction. An EGD needs to be performed in patients with acute vomiting, often for hematemesis or on clinical suspicion of peptic ulcer disease.

Table 6. Comparison of CVS and Chronic Vomiting

Features	CVS	Chronic Vomiting
Age	3.7–6.9 yr	7–8 yr
Female : male ratio	3:1	1:1
Onset of episodes	Nocturnal	Any time of the day
Prodromal autonomic symptoms	Common	Uncommon
Etiology	Non-GI causes = 65%	GI causes = 72%
Frequency of episodes	<9 episodes per month (Q2 wks to Q3 months)	≥9 episodes per month (approximately 36 episodes per month)
Number of emeses per hour	>4 emeses per hour (11–14 per hour)	<4 emeses per hour (1.5 per hour)
Serum chemistries	Abnormal in 14%	Abnormal in 2%
Leukocytosis	3%	2%
Family history of migraine	40–60%	11–14%

Ref: (1, 16, 17).

If the above tests are negative, structural lesions need to be excluded with imaging studies such as head and abdominal/pelvis CT. An EEG may be obtained depending upon the clinical suspicion of seizure disorder.

In the case of patients presenting with cyclic symptoms of vomiting, metabolic disorders including pituitary-adrenal disorders, organic acid, and amino acid disorders need to be screened for.

A common diagnostic dilemma is to differentiate CVS from chronic vomiting. Most patients with the chronic vomiting do not have a cyclic pattern, are less likely to have autonomic symptoms, usually vomit less then four times an hour, and often have no family history of migraine headaches (see Table 3). When a patient—a child or adult—with known CVS is seen during an episode, the physician must still consider other potential etiologies of vomiting for the current episode (41–50) (Table 6).

TREATMENT

No standard evidence-based regimen currently exists to manage CVS (1, 13). Most of the information in the literature is based on anecdotal evidence, and what is published has been developed primarily for children. Thus, guidelines for adults with CVS must be adapted from pediatric recommendations. Treatment is usually individualized and often is a trial and error process (15). Management is based on the four phases of CVS. Treatment is applied according to the phase the patient is in at the time of presentation. The therapeutic goal during the interepisodic phase is prophylaxis of further episodes. The goal during the prodromal phase is to abort the oncoming vomiting phase. The goal during the vomiting phase is to prevent dehydration and terminate the nausea and vomiting or, failing that, to make the vomiting stop and the patient insensible to their misery by intravenous sedation. The goal of the recovery phase is to refeed the patient without causing a relapse of nausea (51).

Prophylactic Therapy to Prevent CVS

Prophylactic therapy is given to patients between episodes to prevent cyclic vomiting. It is advisable if CVS episodes are frequent, difficult to abort, or cause significant morbidity leading to excessive absenteeism from work or school (52, 53). Along with medical therapy, predisposing factors (see Table 2) should be identified and corrected (13, 15, 52). Prophylactic antimigraine medication should be considered, especially if patient has a family history of migraine headaches or if the episode is associated with symptoms of photophobia, phonophobia, scotomas, headache, or diplopia (13, 53). Medications used for prophylaxis include cyproheptadine (54), propranolol (55, 56), and tricyclic antidepressants (*e.g.*, amitriptyline (56, 57), doxepin, and nortriptyline). 5HT1d agonists (*e.g.*, sumatriptan, eletriptan) are specific therapy for migraine headache, should it develop in any phase of CVS, but there is little evidence for their efficacy in ameliorating gastrointestinal symptoms during the prodromal or vomiting phases.

In patients who are sleep-deprived, restoration of a normal sleep pattern aids in preventing attacks. T-ricyclic antidepressants may be helpful in CVS patients due to an identified high association of depression and anxiety disorders (12, 13, 51, 54) (Table 7).

Other drugs for CVS may be tailored to possible pathophysiologic causes. For example, ketorolac and indomethacine have been shown to be beneficial in patients with hyperadrenal activity and endogenous prostaglandin release as a possible cause for CVS (30).

If a CVS patient has an abnormal EEG, antiepileptic drugs such as phenobarbital, carbamazapine, and pizotofen have been shown to be effective (58, 59).

Table 7. Adult and Pediatric Phenotype

Features	Pediatric Phenotype	Adult Phenotype
Age of Onset	3.7–5.2 yr	31–39 yr
Median delay in diagnosis	2–4 yr	5–11 yr
Duration of each episode	1.5–2.5 days	3.5–4.2 days
Family history of migraine	40%	24%
Clinically significant dehydration	80%	30%

Ref: (1, 2)

Erythromycin, a prokinetic motilin agonist, has been successful in preventing some CVS attacks in some patients but selection criteria are not well established (31).

Abortive Therapy for CVS

Abortive therapy is used during the prodromal phase when the patient begins to sense early nausea signaling the approach of vomiting, but is still able to take and retain oral medications (13, 20, 53).

Patients prefer a dark, quiet nonstimulating environment (15), which can be initiated as soon as any prodromal signs occur. Many antiemetic agents have been proven to be clinically beneficial; specifically, agents such as ondansetron and promethazine in combination with diphenhydramine have been successful. Benzodiazepines may be required to help induce sleep, which may then terminate the episode (13, 53). Symptomatic treatment for pain, hypertension, diarrhea, headache, and heartburn may also be necessary.

Treatment During the Vomiting Phase

The possible complications of the vomiting phase include hypovolemic shock, electrolyte depletion, tetany, hematemesis, and secretion of inappropriate antidiuretic hormone. The nausea and other symptoms are agonizing. Therefore, treatment of CVS episodes must be prompt, ideally within an hour of onset. "Watchful waiting" or long waits in treatment facilities are counter-therapeutic. Dehydration requires intravenous correction. Serotonin antagonists, *e.g.*, ondansetron, may be administered as soon as restoration of intravascular volume is well under way. When the patient is normovolemic, attempt to terminate the vomiting phase with intravenous lorazepam and ondansetron. If the patient is experiencing severe, abdominal migraine-like pain (which is typically intense, midline, and noncolicky) and/or symptoms of panic (13), a one-time parenteral dose of hydromorphone produces almost immediate relief. If these measures abolish the symptoms of the vomiting phase, and if relief is sustained, the episode will have been terminated.

If the episode cannot be terminated, the patient must then be relieved by being sedated (51). Administer sedative agents intravenously that are preferably nonaddictive (*e.g.*, chlorpromazine combined with diphenhydramine) and repeat the sedative infusion as needed whenever the patient wakens with nausea, until the episode ends. The nauseated patient is intolerant to noise, bright light, and being moved about. Try not to interrupt sleep for routine vital signs and other procedures. If possible, wait for spontaneous awakenings at which time the patient can void, urine can be collected for determinations of specific gravity (screening for SIADH), and vital signs can be measured. The finding of hypotension should caution against further administration of sedative agents having vasodilatory side effects until blood pressure has returned to normal.

Psychiatric Aspects of Care

Two distinct phenomena comprise the predisposition to CVS in most patients: the migraine diathesis and anxiety. The majority of patients fall between these two extremes and have elements of both predispositions (15).

Of the three sources of anxiety mentioned above (the burden of illness, anticipatory anxiety, and preexisting psychological trauma), the first two can be ameliorated by provision of 5 elements of care: (a) an experienced, accessible, responsive clinician; (b) effective medications; (c) a rational plan for the deployment of such medications (51); (d) promptness in the provision of care when the patient is in distress; and (e) the availability of a reliable "escape" procedure to relieve episodes that cannot be prevented, aborted, or terminated.

Finding adequate care has been difficult for CVS patients. One reason for this is lack of familiarity with the disorder within the medical community, a problem that is beginning to be addressed. Another reason is that CVS tends to be a "high maintenance" clinical problem; there are as yet no evidence-based guidelines for management that work for most patients. Treatment needs to be individualized, a process that can consume much time and effort. CVS is not simply a migraine equivalent. The efficacy of prophylactic and ameliorative agents depends on the appropriateness of the match-up between the therapeutic agents administered (*e.g.*, antimigraine, antianxiety, or both) and the pathogenic factors affecting each individual patient. Moreover, the tractability of CVS in patients who are predisposed to attacks by preexisting anxiety disorders largely depends on the tractability of their psychiatric illnesses. CVS with episodes triggered by panic attacks in a patient with posttraumatic stress disorder, for example, may be quite challenging because his/her psychiatric disorder is not easily resolved with psychiatric care.

Nevertheless the help of a mental health professional experienced with CVS can be useful for the entire family in selected patients (20).

PROGNOSIS

Several studies have attempted to address the natural history of patients with CVS. However, consistent long-term follow-up is not available in most studies. Shared observations suggest that the majority of patients cease to have emetic episodes and remain asymptomatic whereas some patients appear to transform emeses to migraine headaches.

In the series by Hoyt and Stickler (60), follow-up was available for 38 of 44 patients. During the follow-up interval, 30 (68%) patients had ceased to vomit and of the 8 patients who had recurrent vomiting, the follow-up interval was less than 5 yr. Importantly, 14 (37%) of the 38 patients developed recurrent headaches, with most being diagnosed as migraine. Fleisher and Matar (15) had follow-up data available for 29 of 71 patients in their series and 16 of these 29 patients (55%) were asymptomatic for more than 1 yr at follow-up.

Li and Hayes (19) evaluated 88 children in their series of 277 patients with CVS who were disease free. CVS was defined as being resolved if the symptom-free period lasted more than 12 months. Two-thirds of these patients did not have any symptoms and one-third developed migraine

headaches at the follow-up. Seven percent developed abdominal migraines while 5% progressed through all three disorders: from CVS to abdominal migraines to migraine headaches. However, the young age at onset in pediatric patients with CVS is likely correlated with a longer duration of illness. For age at CVS onset less than 3 yr, 3–8 yr, and greater that 8 yr reported lengths of illness are 5.8 yr, 4.9 yr, and 2.9 yr, respectively and about 75% of patients eventually cease to vomit and have migraines by 18 yr of age.

Josephine Hammond (61) evaluated 12 adults between the ages of 17 and 27 who had CVS during childhood. Results indicated that 6, 7, and 8 patients had abdominal pain, vomiting, and headache, respectively, up to 10 yr later, supporting the conclusion of others that children with CVS often have symptoms well into adulthood and that many later develop headaches.

SUMMARY

CVS is a functional vomiting disorder that affects individuals of all ages. CVS itself is intermittent and is punctuated by variable duration of asymptomatic periods. Clear etiology is yet to be identified but present evidence points to maternal inheritance and mitochondrial DNA mutations in some. A large number of CVS patients and/or family members are affected by other similar episodic disorders of unknown etiology often with features of dysautonomia. Advanced CVS symptoms are more difficult to treat; therefore, clinicians should start symptomatic treatment as soon as possible after ruling out other potential life-threatening causes of vomiting. Some CVS patients live relatively normal lives and are free of symptoms in their adulthood while others develop either abdominal migraine or migraine headaches. Renewed interest and research shall lead to more knowledge and insight into CVS symptoms as well as better options for prevention and treatment in the future.

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CONFLICT OF INTEREST

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