

Extreme Emesis: Cyclic Vomiting Syndrome

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Cyclic vomiting syndrome (CVS) is an idiopathic disorder that has been primarily identified in children but has recently been increasingly recognized in adults. Acute episodes are typically misdiagnosed as gastroenteritis and food poisoning that leads to a three-to-eight year delay in diagnosis. The major challenge for the frontline clinician is to differentiate CVS, a functional disorder without laboratory markers, from the myriad organic causes of vomiting. Better awareness and earlier recognition and treatment of CVS will reduce the morbidity, avoid unnecessary investigations and repeated hospitalizations that are estimated to incur \$17,035 per patient annually (1). This article focuses on the clinical features, including differences between adults and children, potential pathophysiologic mechanisms, pertinent exclusionary investigations and specific treatment approaches.

INTRODUCTION

Cyclic vomiting syndrome was first described by Samuel Gee in 1882 (2) and named cyclic vomiting by Smith in 1937 (3). CVS is characterized by recurrent, sudden, stereotypical, disabling, discrete episodes of intense nausea and vomiting that can last a few hours to days interspersed with varying weeks of symptom-free intervals.

EPIDEMIOLOGY

The estimated prevalence of CVS in children is in the range of 0.3%–2.2 % (4). This disorder is primarily

recognized in children, primarily Caucasians (mean age of onset at five years), with increasing recognition in adults (mean age of onset at 35 years). There have been case reports of symptoms starting as early as the sixth day of life and as late as 73 years. In children, females appear to be more affected than males, compared to a male predominance in adults (5,6).

PATHOPHYSIOLOGY

CVS is now considered to be a functional brain-gut disorder in which central signals initiate a peripheral gastrointestinal manifestation—vomiting. There appear to be a number of host susceptibility factors including a family member with migraine headaches (82% of CVS versus 14% of chronic vomiting patients), mitochondrial dysfunction, and autonomic dysregulation. There is a strong matrilineal inheritance of CVS from migraines, elevated lactic acid, and several heteroplasmies in the control region of the mtDNA supporting involvement of mtDNA (7,8). There is also heightened sympathetic cardiovascular tone in children with CVS compared to controls (9,

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Table 1
Difference Between Chronic and Cyclical Pattern of Vomiting

	<i>Cyclic or Episodic</i>	<i>Chronic</i>
Intensity of vomiting	High (≥ 4 emesis/hour at the peak)	Low (1–2 emesis/hour)
Frequency of vomiting	Low (1–2 episodes/month)	Nearly daily
Diagnoses	Highly supportive of CVS or disorders outside the GI tract (e.g., hydrocephalus)	GERD or gastritis (disorders of the upper GI tract)
Dehydration	Common	Uncommon

10). These factors taken together suggest that inadequate cellular energy production at times of heightened needs (trigger factors mentioned below) leads to a metabolic crisis. This in turn leads to a deleterious effect on high energy requiring autonomic neurons resulting in an episodic autonomic crisis with vomiting. Similar to migraines, there appear to be common triggering factors including psychological stress (especially excitement) and infections. Based largely on extensive animal studies, Taché, et al have proposed that the hypothalamic secretion of corticotrophin-releasing factor (CRF) could act as the neuroendocrine trigger of vomiting (11). CRF stimulates the inhibitory fibers of the dorsal motor nucleus of the vagus decreasing the upper GI tract motility (and potentially triggers vomiting). By also acting on the locus ceruleus, CRF also increases sympathetic tone and the associated signs of pallor, flushing, fever, lethargy, excess salivation, and diarrhea.

CYCLIC VERSUS CHRONIC PATTERNS OF RECURRENT VOMITING

The key to diagnosis of CVS is recognition of the cyclic pattern of these repeated vomiting episodes. Recurrent vomiting can be divided into two temporal patterns described as either cyclic or chronic (Table 1).

The cyclic pattern is highly supportive of an eventual diagnosis of CVS, once the radiographic, laboratory and endoscopic evaluations are negative. The chronic pattern usually indicates a disorder such as gastroesophageal reflux or gastritis within the upper GI tract (12). It is also important to recognize that CVS is but one of the causes of a cyclic vomiting pattern. Other causes of severe episodic vomiting in children include

surgical lesion (malrotation with intermittent volvulus), metabolic (acute intermittent porphyria) and endocrine disorders (Addison disease) (13). CVS is frequently misdiagnosed in emergency departments as rotavirus gastroenteritis and food poisoning; however patients with CVS are qualitatively (pallor, listlessness) and quantitatively (more likely to require IV rehydration) sicker (6) than patients with rotavirus infections.

DIAGNOSTIC CRITERIA

CVS is currently defined by fulfilling “essential and supportive” criteria. The Consensus diagnostic criteria for CVS in children (14) and adults (15) are shown in Table 2A and 2B.

CLINICAL FEATURES

Typical CVS episodes tend to have a stereotypic pattern within individuals and can be subdivided into four phases (16). The initial prodromal phase before the onset of vomiting often begins suddenly with symptoms of nausea, sweating, abdominal pain, irritability and anorexia. However, they usually do not have visual symptoms of typical migraine aura. The prodrome is often brief and rapidly progresses to vomiting within one-to-two hours. The second phase is the emetic phase characterized by relentless nausea and vomiting and persistence of the prodromal symptoms. The unique rapid fire (often every five-to-ten minutes) vomiting often begins early in the morning between 2–4 A.M. or upon awakening at 7 A.M., although in some episodes start later. The vomiting episodes last for one-to-three days in children and six-to-nine days
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Table 2A
Consensus Diagnostic Criteria in Children

Essential criteria

- Recurrent, severe, discrete episodes of vomiting
- Varying intervals of normal health between episodes
- Duration of vomiting episodes from hours to days
- No apparent cause of vomiting (negative laboratory, radiographic and endoscopic testing)

Supportive criteria

- Pattern
 - Stereotypical: each episode similar as to time of onset, intensity, duration, symptoms and signs within individuals
 - Self-limited: episodes resolve if left untreated
- Associated symptoms
 - Nausea, abdominal pain, headache, motion sickness, photophobia, and lethargy
- Associated signs
 - Pallor, dehydration, fever, excess salivation and social withdrawal

in adults (17,18). Symptoms of anxiety and panic attacks appear to be common in adults during the first two phases. The patient may be so listless as to appear in a coma-like state, unable to ambulate or speak. The third phase is the recovery phase which begins with the disappearance of nausea and vomiting to the point of return of near normal appetite and activity. This may be brief, like the prodromal phase, so that the patient appears to suddenly awaken like “turning off a switch” and be able to eat within one-to-two hours of cessation of emesis. The fourth phase is the well-interval phase during which the patient is symptom-free. In children, there may be four weeks to several months of normal health. This differs from adult patients in whom some 50% have significant symptoms, usually dyspeptic nausea and/or sporadic vomiting in between. This has been called coalescence of episodes. Recent studies indicate that 70% of adult patients have psychological co-morbidities and a previous diagnosis of or features characteristic of, one or more of the following: anxiety (63%–84%), panic attacks (68%), depression (78%), alcoholism and/or drug abuse (5,16). An unpublished report in children estimates a high prevalence of anxiety (39%) and mood symptoms in children compared

Table 2B
Diagnostic Criteria* in Adults

- Must include all of the following
 - Stereotypical episodes of vomiting regarding onset (acute) and duration (less than one week)
 - Three or more discrete episodes in the prior year
 - Absence of nausea and vomiting between episodes
- Supportive criterion
 - History or family history of migraine headaches

*Criteria fulfilled for the last three months with symptom onset at least six months before diagnosis

to norms of the Children’s Symptom Inventory and population normal for internalizing psychiatric disorders (Dr. Sally Tarbell).

OTHER FEATURES

Some patients complain of intense abdominal pain requiring narcotics for relief and/or severe headaches. Others may present with low-grade fever, vomiting, and diarrhea that is easily confused with acute viral gastroenteritis. Hypertension with tachycardia has also been observed in a subgroup with a more severe (prolonged) variant of CVS described by Sato, et al (19,20). The intense nausea experienced during the emetic phase of CVS has induced behaviors that have been mistakenly considered bulimic or psychotic. For example, intense thirst has been reported in some adult patients drinking as much as 14 liters of water in a day, yet this has been described by patients to attenuate the nausea. Dehydration with electrolyte abnormalities ($^-Na^+$, $^-K^+$, $^-CO_2$), hypoglycemia, and gastrointestinal bleeding secondary to prolapse gastropathy, Mallory-Weiss tear or esophagitis are some of the frequent complications of CVS. The main differences between adult and children with cyclic vomiting syndrome are shown in Table 3.

PRECIPITATING FACTORS

Two-thirds of families are able to identify events that appear to precipitate a child’s episode (21–23). The two most common triggers are infections of any kind (31%), particularly chronic sinusitis, and stress (47%)

Table 3
Comparison of CVS Clinical Features Between Children and Adults

	<i>Children (Li/Balint)</i>	<i>Adults (Fleisher/Namin)</i>
Age of onset	4.8 years (earliest: 6 days)	30–35 years (oldest: 73 years)
Delay in diagnosis	2.6 years	8 years
Female:Male	57:43	30:42
Episodes pattern		
Frequency	every 2–4 weeks	every 3 months
Duration (range)	1–2 days (1–10)	4–6 days (1–21)
Periodicity	49%	not reported
Early A.M. onset	42%	50%
Stereotypical	99%	85%
Prodrome	72%, 1.5 hours	93%
Symptoms	nausea, anorexia, pallor	nausea, epigastric pain
Recovery to oral feeding	6 hours	24 hours, 10 days
Relieving factors	deep sleep	hot bath/shower (56%–72%)
Precipitating factors	stress (47%), infection (31%)	stress (50%), menses
Co-morbid conditions	anxiety	anxiety, panic attacks, migraine, depression
Inter-episodic nausea	<6%	63%
Coalescence of episodes	few	50%
Symptoms		
Vomiting	6 times/hr at peak, bile (81%)	8.5 times/hr, bile
Systemic	pallor, salivation, listlessness,	intense thirst (33%)
GI	anorexia, nausea, diarrhea, abdominal pain	abdominal pain, diarrhea
Neurologic	headache, photophobia, phonophobia, vertigo	irritable, confused
Natural history	3.6 years	5.2 years
FH of migraine	28+% progress to migraine	23%–57%
Complications	dehydration, esophagitis	dehydration, esophagitis, laprotomy (18%)
Morbidity	14–25 days of missed school/year	32% completely disabled before initiating therapy

at school or home. Interestingly, the most common scenario was positive excitement that included birthdays, holidays and family reunions. The most frequent triggers in adults are menstrual periods, noxious stress, pleasant excitement and fatigue.

NATURAL HISTORY

In children, CVS often resolves by early puberty. Approximately 28% of patients with CVS have migraine onset at 9.5 years and it is projected that 75% will develop migraines by age 18. In a cross-sectional school survey by Abu-Arafah and Russell, the mean respective ages of children with CVS, abdominal

migraine, and migraine headaches are 5.3, 10.3 and 11.5 years suggesting a sequential progression among the three entities (24). Although some do experience all three phases, most children with CVS develop migraine headaches without passing through an intervening abdominal migraine stage. In a series of 41 adult patients studied by Fleisher, the natural history differed substantially from that in children as nearly half of the adult patients experienced deterioration over time either by the coalescence of episodes or development of chronic inter-episodic dyspeptic nausea. One-third of adults were completely disabled and required financial support at the time of initial consultation before therapy was initiated (16).

Table 4
Differential Diagnosis of Cyclic Vomiting Pattern by Relative Frequency

		<i>Children</i>	<i>Adults</i>
Gastrointestinal	Inflammatory bowel disease	+	++
	Malrotation with volvulus	+++	+
	Chronic intestinal pseudo-obstruction	+	++
	Partial intestinal obstruction	+	++
	Neoplasms	–	+
	Cholelithiasis	+	++
	Recurrent pancreatitis	+	++
Genitourinary	Hydronephrosis 2° UPJ obstruction (Dietl crisis)	+++	–
	Nephrolithiasis	+	+
Central nervous system	Hydrocephalus	+	+
	Arnold-Chiari malformation	++	–
	Subtentorial neoplasm	+	–
	Familial dysautonomia	+	–
Metabolic	Disorders of fatty acid oxidation	+	–
	Acute intermittent porphyria	+	++
	Urea cycle defects	+	–
	Mitochondrial disorders	+++	–
Endocrine	Addison disease	+	+
	Pheochromocytoma	+	+
	Diabetic gastroparesis	+	++
Psychological	Munchausen syndrome-by-proxy	+	–
Other	Pregnancy	+	+
	Drugs and medication	–	++

DIFFERENTIAL DIAGNOSIS

The major challenge is to differentiate CVS, a functional disorder from the myriad organic causes of vomiting. Although the cyclic vomiting pattern usually indicates the diagnosis of cyclic vomiting syndrome in 88%, approximately 12% of children who presented with the typical cyclic pattern were found to have a specific, underlying cause for their vomiting (Table 4). The differential diagnosis is broad both in children and adults. Since structural and metabolic conditions typically present in childhood, especially acute hydronephrosis and malrotation with volvulus, more extensive testing for renal, GI, intracranial, metabolic and endocrine disorders has been applied to children (25).

DIAGNOSTIC INVESTIGATIONS

To date, how much exclusionary testing should be per-

formed in patients with the cyclic vomiting pattern is unclear. The typical approach in children and adults has been a shotgun approach to perform extensive laboratory, radiographic and endoscopic testing in a patient with a cyclic vomiting pattern to exclude an underlying structural, endocrine or metabolic lesion. For example, in a retrospective review of 39 adult patients by Fleischer, multiple studies with normal findings (EGD, UGI and abdominal ultrasound) were obtained on each patient (16). However, based on the relatively low-yield of testing children (27 of 225 = 12%), more cost-effective approaches have been proposed. A cost-decision analysis showed that the most cost-effective approach to the initial treatment of children with cyclic vomiting pattern is to make a tentative diagnosis of CVS, perform a single UGI radiograph to exclude malrotation, and begin a two-month empiric

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Table 5
Alarm Symptoms, Potential Diagnosis, and Testing in CVS Patients

<i>Alarm Symptoms</i>	<i>Potential Diagnosis</i>	<i>Screening Tests</i>
Abdominal distension, abdominal pain/bilious emesis	Intestinal obstruction Intermittent UPG obstruction	UGI US abdomen (28)
Episodic vomiting induced by fasting, illness or diet	Mitochondrial or metabolic problem	Metabolic testing
Altered mental status or gait, focal or diffuse neurological abnormalities, early morning vomiting or papilledema	Subtentorial neoplasm Chiari malformation	MRI brain

trial of anti-migraine medication (26). The upcoming pediatric consensus guidelines (27) on the management of CVS suggest that unless an alarm symptom (Table 5) is present, only a chemistry profile (during the episode) and UGI x-ray to exclude malrotation need be performed initially. However, if alarm symptoms are present or continuous, worsening or nonresponsive symptoms, one should either consider or repeat CT or ultrasound of the abdomen during the episode. There have been no established guidelines for diagnostic evaluation in adults.

TREATMENT

The treatment in CVS is largely empiric and involves: a) lifestyle changes, b) prophylactic (antimigraine and anticonvulsant) therapy, c) abortive antimigraine therapy, and d) supportive and symptomatic treatment during episodes. Patients and families are often greatly relieved when the physician identifies CVS as diagnosis and can reassure them that it is not a life-threatening disease. In explaining this mysterious disorder, the physician can draw an analogy to other disabling functional conditions, such as irritable bowel syndrome or even migraines, for which there is no known cause or confirmatory test, but are nevertheless valid diagnoses for which there is reasonable treatment. The physician can then help the family to design a collaborative strategy for preventing and responding to future episodes that will expedite the treatment. Because this disorder is so difficult to treat, a few centers have developed and use a multidisciplinary team featuring a gastroenterologist and nurse, as well as a neurologist and a psychologist.

Recognition and Avoidance of Triggers

A careful history or patient diary can identify triggers such as specific stressors or foods (e.g. chocolate, cheese, MSG) that if avoided may reduce the frequency of episodes. As psychological stress is a well documented trigger in children and adults, psychological counseling and stress reduction techniques may also help. An Australian study reported an association of cyclic vomiting illness with chronic cannabis use with resolution of cyclic vomiting illness after withdrawal from cannabis use (29).

Prophylactic Therapy

Prophylactic therapy taken daily to prevent subsequent episodes has been recommended if the patient has the following characteristics: higher frequency (e.g. >1 episode/month), greater severity (frequent hospitalization), longer duration (e.g. >24 hours) or poor response to abortive therapy. Prophylactic agents include antimigraine medications, anticonvulsants and prokinetics (erythromycin) (30). Antimigraine prophylaxis is more effective in children who have a family history of migraine. In the NASPGHAN Guidelines for children, cyproheptadine is recommended as first line therapy in children <5, and amitriptyline for over five years of age, with propranolol serving as second line (27). These three agents have been shown to decrease the number or severity of episodes by 47%, 75%, and 52% respectively (31). In adults, tricyclic antidepressants (TCA) are the most commonly used agents with amitriptyline doses of up to 100 mg daily required for the desired therapeutic effect. Recently Clouse, et al reported the effective use of levetiracetam or zonisamide as prophylactic agents in adults (32). Other

Table 6
Therapeutic Approaches to Cyclic Vomiting Syndrome

SUPPORTIVE THERAPY—Children and Adults		Side-effects
Fluids	D5/0.5 NS 10 cc/kg bolus + 1.5 maintenance D5/0.2NS + KCl	
Antiemetics	Ondansetron IV 0.3–0.4 mg/kg q 4–6 h Granisetron IV 10 µg/kg q 4–6 h	Contraindicated in liver disease Headache, dizziness, constipation
Sedatives	Lorazepam IV 0.05–0.1 mg/kg q 6 hrs Chlorpromazine IV 0.5–1.0 mg/kg q 6–8 h Diphenhydramine IV 1 mg/kg q 6h	Respiratory depression, agitation Dystonic reactions, hypotension Prevents dystonic reactions
Analgesics	Ketorolac IV 0.5–1.0 mg/kg q h <30 mg Narcoics	Gastrointestinal ulcerations/GI bleeding Respiratory depression, hypotension
ABORTIVE THERAPY		
	Sumatriptan NS mg or SQ 6 mg Zolmitriptan 5 mg nasally	Chest burning, contraindicated in ischemic heart disease As above
PROPHYLACTIC THERAPIES (PO daily)		
Children	Cyproheptadine 0.3 mg/kg/d div. bid-tid Propranolol 0.6–1.5 mg/kg/d div. bid-tid Amitriptyline 0.5–1.0 mg/kg qhs	Titrate dose every 2–4 weeks 1st line <5 yrs, side effect—weight gain 2nd line, monitor resting heart rate (keep >55/minute) 1st line >5 yrs, check QTc before starting and 10 days after the peak dose
	Phenobarbital Erythromycin Low estrogen birth control (catemial CVS)	Learning difficulties Abdominal cramps Thromboembolism, hypertension
Adults	Amitriptyline, nortriptyline Zonisamide Levicetiram	Narrow therapeutic index Fatigue, dizziness, kidney stones Somnolence, muscle weakness

antiepileptics (topiramate) and mitochondrial supplement such as L-Carnitine (33) and Co-enzyme Q10 have demonstrated efficacy in reducing the frequency of migraines and may have a future role in CVS prophylaxis.

Abortive Therapy

Antimigraine medications are used to attempt to terminate breakthrough episodes. Antimigraine triptans, sumatriptan and zolmitriptan both of which can be administered intranasally to circumvent vomiting and loss of oral medication. Sumatriptan, a serotonin (5-HT_{1B/1D}) agonist when administered either by intranasal or subcutaneous route has a 46% efficacy in children (34). Sumatriptan is usually either highly

effective and stops the episode completely within two hours or does not alter the episode at all. If that fails, one can proceed to supportive therapy.

Supportive Therapy

Once an acute episode begins or breaks through prophylactic therapy, it usually is refractory to treatment and proceeds along its usual course and duration. The goal is then to reduce the extreme discomfort by attenuating the nausea, vomiting and pain. This management includes reducing stimulation in a quiet, dark room with minimal vital signs because these patients are hypersensitive to light, sound, and even touch. Administration of

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5%–10% IV dextrose with NaCl and KCl will correct fluid and electrolyte deficits, hypoglycemia and ketosis. 5HT₃ antagonist antiemetics such as ondansetron administered at high dose (0.3–0.4 mg/kg/dose ≤25 mg/dose) appear to be much more effective than D2 antagonists (e.g. prochlorperazine) (Table 6). By achieving sleep, sedatives such as lorazepam can further alleviate the unrelenting nausea. For severe pain, either Ketorolac or narcotics (e.g. hydromorphone or morphine) have been used. Often because of the unremitting episodes, these agents are used in combination.

SUMMARY

CVS is an increasingly recognized disorder both in children and adults. Increased awareness of the condition and a high index of suspicion may help decrease delay in diagnosis after symptom onset. A guide is provided here for clinicians who are challenged with the prospect of detecting and evaluating the patient with CVS. Care needs to be delivered by a physician who is somewhat familiar with this disorder and in a nonjudgmental manner. The Cyclic Vomiting Syndrome Association (www.cvsa.online) also provides support with a website, literature, electronic bulletins, phone and email to help children, adults and their families with this difficult disorder. The scarcity of research found in this area indicates further research is needed. ■

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