Cyclic Vomiting Syndrome, Part 1

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Cyclic vomiting syndrome (CVS) is a potentially incapacitating disorder that affects all ages. It was first recognized in children but is increasingly documented in adults as well. The prevalence in adults is currently unknown and its pathophysiology remains speculative. In adults, CVS may be a primary disorder, secondary to systemic disease, or a consequence of cannabinoid abuse. Therapy is symptomatic and includes tricyclic antidepressants, triptans, nonsteroidal anti-inflammatory drugs, benzodiazepines, and antiemetics. Some patients with CVS have increased psychiatric comorbidity with anxiety or depression. This column provides an overview and history of CVS, its epidemiology, the clinical features in children and adults, and the Rome III diagnostic criteria. Part 2 will review a particular variant of CVS (cannabinoid hyperemesis) as well as psychiatric aspects of the illness, its pathophysiology, differential diagnosis and diagnostic evaluation, treatment, and prognosis.

OVERVIEW

Over the past century, the term “psychogenic or nervous vomiting” was used by gastroenterologists as well as psychiatrists as a diagnosis for patients with chronic, recurrent vomiting of unknown cause. Forty years ago, Hill observed that there were factors acting as “general sources of stress and strain... in person otherwise predisposed to vomit.”

Etiologic clarification of the roles of stress and predisposition in chronic recurrent vomiting is an ongoing focus of investigation. The clinical entity of CVS was first recognized in children, and only later in adults. Interest in the syndrome was stimulated when Kathleen Adams, a parent of an affected child, founded the Cyclic Vomiting Syndrome Association in 1993, to provide support for affected families as well as increase physician awareness and the need for more research.

The diagnosis of CVS in adults was finally added in 2006 to the Rome III classification of functional gastrointestinal (GI) disorders.

CVS is characterized by episodes of high-intensity nausea and vomiting lasting for several days, recurring several times per year, with symptom free intervals in between episodes. Since first described in the French literature by Heberden in 1806 and in English literature by Gee in 1882, cyclic vomiting was mainly recognized as an entity in children. However, it has become evident that adults too can suffer from episodic vomiting. It would be reasonable to view the adult and childhood forms of the disorder as one continuum, but this has not been established. Rather, it seems that there are several different pathophysiologic routes to the same syndromal presentation, activated at different ages.

CVS is frequently accompanied by anxiety, panic attacks, and depression, in adults as well as children. Nausea and vomiting are familiar accompaniments of emotional distress, as reflected in common expressions such as “You make me sick” or “I am fed up.” In CVS it is puzzling why a natural defensive mechanism which functions to eliminate ingested toxins becomes intensely hypersensitive and hyperactive.

Recent research suggests a variety of possible etiologies, including cannabinoid hyperemesis, mitochondrial enzymopathies, corticotropin releasing factor-adrenocorticotropic hormone axis dysfunction, GI dysmotility, autonomic nervous system dysfunction, and genetic factors. The frequent association of CVS with migraine suggests the possibility of shared pathophysiology.

Physicians who become frustrated when thorough, repeated investigations of the GI tract fail to find an explanation for CVS often conclude “there is something wrong in the patient’s...
head.” They might actually be right, but at a neural level rather than a psychological one. However, it is well known that psychosocial factors act as a trigger for CVS. Clinical experience and literature confirm that addressing anxiety, panic attacks, depression, and/or migraine can be a successful strategy in helping patients with CVS. Of course, the roles of biologic and psychosocial factors are not mutually exclusive.

**EPIDEMIOLOGY**

CVS affects all races and ethnicities but is more common in Caucasians. CVS has been reported in children as young as 6 months of age and in adults as old as 73 years of age. The prevalence in adults is not known. The reported prevalence in children has ranged from 0.03% in Ireland to 1.9% in Turkey. Both of these studies found CVS more common in girls (57:43 in Ireland, 67:33 in Turkey), but other studies did not report any significant gender differences in prevalence. Many characteristics of the CVS are similar irrespective of age of onset.

**CLINICAL FEATURES**

CVS is characterized by four phases. The prodromal or pre-emetic phase typically lasts minutes to hours, with nausea, abdominal pain, lethargy, anorexia, and pallor. The patient is able to manage oral intake without vomiting. This is followed by the emetic phase, lasting hours to days, with high-intensity nausea, repeated vomiting (sometimes >20 times/hour), intense thirst, irritability, abdominal pain, and prostration. In the recovery phase, lasting minutes to days, vomiting stops and hunger, food tolerance, and a sense of well-being return. Finally, there is the well or interepisode phase, lasting weeks to months, in which the patient is relatively symptom free.

**CVS IN CHILDREN**

In 1882, Gee described a syndrome of recurrent vomiting in children:

These cases seem to be all the same kind, their characteristics being fits of vomiting, which recur after interval of uncertain length. The intervals themselves are free from signs of disease. The vomiting continues for a few hours or a few days. When it has been severe, the patients are much exhausted. In some cases the closest observation fails to discover anything, which can be called the cause.

During the 1930s, >90 articles discussing cyclic vomiting in children appeared in the medical literature. Fatalities were reported, mostly due to dehydration. Since then, interest in pediatric CVS has waned a bit. More recent studies report median age of onset in children is 5–7 years of age, with a delay in diagnosis of 2.7 years. The frequency of episodes varies from 1–70 times/year, with an average of 12 times/year. Two patterns of pediatric CVS have been differentiated—a high intensity form in which peak intensity of vomiting occurs an average of 12.6 times/hour at a mean frequency of 1.9 episodes/month, and a chronic low intensity form with an average of 1.5 emeses/hour at peak intensity at a mean frequency of 36.6 episodes/month.

Episodes most often occur early in the morning (2–4 AM) or upon awakening (6–8 AM). The recovery period from vomiting until being able to eat is ~5 hours. Abdominal pain is present in 80% and can be so severe that a misdiagnosis of acute abdomen and surgical intervention are not rare. Retching is present in 79% and nausea in 82%. Nausea disappears when the child goes to sleep and the episode is over. Other symptoms may include hypersalivation and expectoration, aversion to swallowing, nausea, and induction of vomiting with fingers (to relieve pain).

Frequent comorbid neurologic symptoms, including headache, photophobia, and vertigo, have suggested a relationship between migraine and CVS. Less than 50% of pediatric CVS patients have classic migraine headaches. A family history of migraine headaches has been reported in 40% to 80% of cases. Thus, pediatric CVS may be related to abdominal migraine, itself an uncertain entity.

Children with CVS frequently miss school. Most published series indicate that the disorder lasts 2.5–5.5 years and tends to resolve in late childhood or early adolescence, but some children continue to have CVS into adulthood. In 33% of children, when vomiting disappears it is replaced by migraine headaches.

Apparent triggers for pediatric CVS were identified in 80% in one study, including negative emotional stressors (such as parental conflict) in 54%, and positive ones (such as holidays or birthdays) in 47%. Other triggers reported include upper respiratory infection (31%), exhaustion (24%), dietary change (23%), and menses (22%).

Seventy-five percent of the children with CVS in one study were viewed as having competitive, perfectionistic, high achieving, aggressive, strong willed, moralistic, caring and/or enthusiastic personality traits. Parents have described their children with CVS as happy (68%), moody/shy (21%), anxious (9%), or sensitive (3%). Children and adolescents with chronic illness are known to be at increased risk for emotional and behavioral problems, with the anxiety disorders being most common.
Recent data\textsuperscript{13} support this in children and adolescents with CVS, finding them at increased risk for internalizing psychiatric disorders, especially anxiety disorders. However, most studies have not distinguished which came first—CVS or anxiety; it seems likely that each adversely affects the other.

**CVS IN ADULTS**

While it has long been recognized that pediatric CVS may continue into adulthood, CVS also occurs de novo in adults. There are no prevalence data in adults. The gender ratio appears almost equal. The etiology is unknown and there are no laboratory, imaging, or other physical tests to support the diagnosis. Both the publication of the Rome III diagnostic criteria as well as greater physician awareness about CVS have reduced delay in diagnosis. Several years earlier, delay in diagnosis amounted to ~8–12 years, but it recently has diminished.\textsuperscript{12,13}

Quality of life is significantly impaired, disrupting occupational and social functioning. Frequent visits to the emergency department are frustrating. In the emergency department, patients with CVS may be labeled as “drug seeking,” malingering, or purposely assuming the sick role, or may be misdiagnosed as having bulimia or anorexia nervosa. Patients are often subjected to numerous and repeated tests (eg, endoscopy) and surgical procedures (eg, appendectomy in 18%, cholecystectomy in 23%).\textsuperscript{9,22} If admitted to an inpatient medical unit, the staff may find the patient irritable, hostile, not speaking (due to increased oral salivation), engaging in guzzle and vomit behavior,\textsuperscript{13} and withdrawing in a darkened room.

Severe nausea may respond to antiemetics, but complete relief may be achieved only after induction of deep sleep.\textsuperscript{8,11} The length of the recovery phase ranges from minutes to as long as 22 days.\textsuperscript{13}

Most cases occur in adults 29–49 years of age, with an age of onset of 21–40 years of age, and an average age of 35 years.\textsuperscript{13,22}

CVS attacks are stereotypical for the particular adult, and often have a specific prodrome.\textsuperscript{8,13} The most common prodrome symptoms are nausea, sweating, epigastric pain, fatigue, and weakness.\textsuperscript{13} Precipitating factors have included menstrual period, noxious stress, pleasant experiences, fatigue, and infection.\textsuperscript{12,13} Menstrual periods as a trigger occur in 50% of females with CVS, referred to as “catamenial CVS.”\textsuperscript{12}

Most acute episodes begin between midnight and noon\textsuperscript{13} and are more frequent in the summer. Episodes usually last 3–6 days with the phase of severe vomiting lasting 1–2 days.\textsuperscript{12} The time from severe vomiting to refeeding is ~2 days, somewhat longer in adults than in children.\textsuperscript{12} The cycle interval averages ~3 months.\textsuperscript{13} During an acute episode, the number of emeses ranges from once to 20 times/hour (average=8.5 times/hour).\textsuperscript{13} During the emetic phase, abdominal pain has been reported in 58% to 87%.\textsuperscript{9,12,13}

Severe dehydration (hypotension, diminished skin turgor, and prerenal azotemia) is less common in adults (33%) than in children (83%).\textsuperscript{12} Diarrhea, low-grade fever (100–102°F), leukocytosis, and tachycardia with hypertension each occur in ~20% of patients.\textsuperscript{12,13,23}

A subgroup of patients experience coalescence of the episodes and become sick more days then not, with persistent nausea and vomiting as long as 3 weeks.\textsuperscript{13} One-third of this group of coalescent type are so disabled that they cannot attend work or school.\textsuperscript{13,23} Coalescence appears to be more frequent in untreated patients, or it might be a separate entity.\textsuperscript{23} There is also a variant of CVS in adults with minimal vomiting.\textsuperscript{24}

Migraine headaches have been reported in 24% to 70%, and family history of migraine in ~50% of patients (occurring more often in the matrilineal versus patrilineal family).\textsuperscript{13,22}

**DIAGNOSTIC CRITERIA**

An international panel of clinical investigators reached consensus diagnostic criteria for CVS in the Rome III process in 2006 (Table).\textsuperscript{3}

**TABLE**

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<th>ROME III DIAGNOSTIC CRITERIA FOR CYCLIC VOMITING SYNDROME\textsuperscript{3}</th>
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<tr>
<td><strong>At least 3 months, with onset at least 6 months previously of:</strong></td>
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<td>• Stereotypical episodes of vomiting regarding onset (acute) and duration (&lt;1 week)</td>
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<td>• ≥3 discrete episodes in the prior year</td>
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<td>• Absence of nausea and vomiting between episodes</td>
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<td><strong>Supportive criteria:</strong> History of migraine headaches or a family history of migraine headaches.</td>
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**CONCLUSION**

Part 1 of this review described CVS as a potentially incapacitating disorder affecting both children and adults. Its prevalence and pathophysiology remain uncertain. CVS may be a primary disorder, or secondary to another disease. CVS is characterized by four phases: prodromal, emetic, recovery, and well/interepisode phases. A personal or family history of migraine is very common in CVS patients. CVS is frequently
accompanied by anxiety, panic attacks, and depression. Part 2 will review a particular variant of CVS (cannabinoid hyperemesis) as well as psychiatric aspects of the illness, its pathophysiology, differential diagnosis and diagnostic evaluation, treatment, and prognosis. PP

REFERENCES