

Update in Cyclical Vomiting Syndrome



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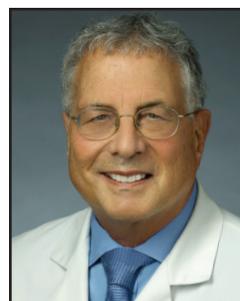
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Cyclical vomiting syndrome (CVS) is a functional idiopathic gastrointestinal disorder characterized by recurrent episodes of severe emesis with periods of remission in between. Since initially termed in 2004, experts continue to try to define the disorder although it is still poorly understood in terms of pathophysiology. Diagnostic evaluation for underlying GI disorder is negative. Treatment has centered around disease recognition including: antiemetics, management coexistent migraine, and cognitive behavioral therapy. Emerging research has investigated the gut axis and neural pathways that may lead to future therapeutic opportunities.

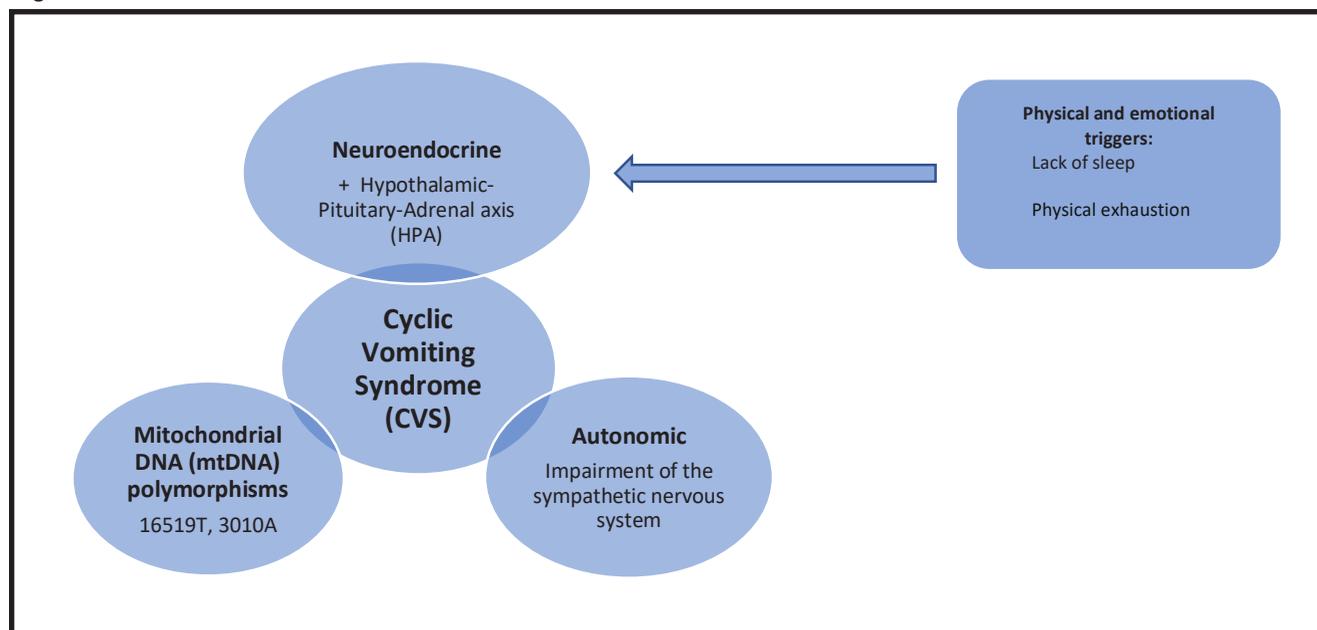
INTRODUCTION

Cyclical vomiting syndrome (CVS) was first described in 1882. Previously thought to only occur in children, CVS has subsequently been described in all age groups. A recent population-based study shows CVS is prevalent in 2% of adults in America.¹ Cyclical vomiting syndrome can be misrecognized and is probably underdiagnosed

causing significant impact on health and quality of life leading to multiple emergency visits and increasing morbidity. Comorbidities such as migraines, trauma, or functional syndromes may help aid in the diagnosis. This paper will review new CVS insights pathophysiology, diagnostic evaluation, and therapeutic opportunities.

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Figure 1.



Pathophysiology

The pathophysiologic process of CVS is unclear. Current theories center around multiple functional disorders involving the brain-gut pathways with central and peripheral nervous system manifestations.² Several mechanisms have been implicated in the development of CVS. In a study using functional brain MRI, the author concluded that although CVS patients had increased connectivity between salience network and mid/posterior insula, CVS and migraine patients displayed close similarities with diminished insular connectivity with the sensorimotor cortex compared to healthy controls.²²

Neuroendocrine Dysfunctions

It is hypothesized that activation of the hypothalamic-pituitary-adrenal axis (HPA) as a result of psychological or physical stress leads to the release of corticotropin-releasing factor (CRF). The release of CRF stimulates the inhibitory motor nerves in the dorsal motor nucleus of the vagus resulting in delayed gastric emptying. Elevated levels of adrenocorticotropic hormone (ACTH), antidiuretic hormone, cortisol, prostaglandin E₂, antidiuretic hormone, cortisol, prostaglandin E₂,

and serum and urinary catecholamines during episodes of CVS was also described by Sato and associates.¹⁹

Autonomic Dysfunction

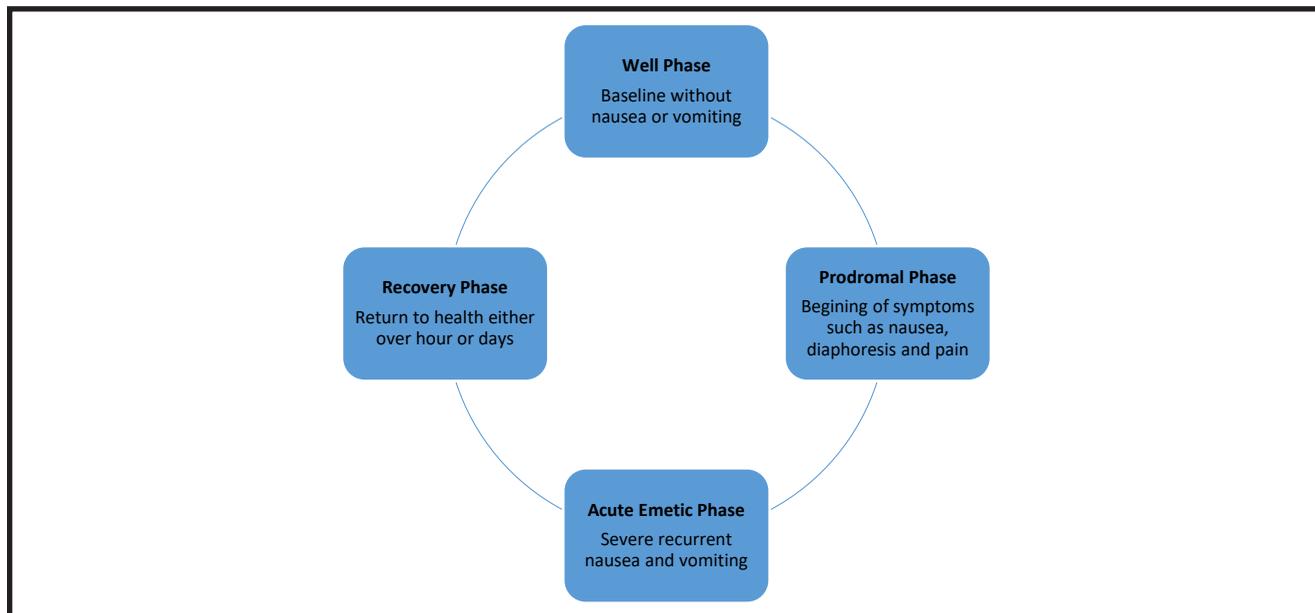
Autonomic mediated symptoms such as pallor, flushing, drooling, diarrhea, and dysmotility are common during episodes of CVS. Role of autonomic dysfunction in the pathophysiology of CVS has been studied in the literature. It was suggested that patients with CVS have impairment of the sympathetic nervous system with intact parasympathetic nerve function.¹⁶ Rapid gastric emptying at baseline, which may be related to autonomic dysfunction, and delayed gastric emptying during episodes have been demonstrated in adults with CVS.²⁰

Mitochondrial Dysfunction

The maternal inheritance of both migraine and CVS suggest mitochondrial dysfunction.

CVS was linked to maternal mitochondrial dysfunction in the pediatric population such as mitochondrial DNA (mtDNA) polymorphisms: 16519T, 3010A.¹⁷ However, the significance of these single nucleotide polymorphisms (SNPs) remains unclear. These mitochondrial associations have not been identified in adults with CVS suggesting other

Figure 2.



genetic factors in adults. Mitochondrial dysfunction is exacerbated by cellular energy depletion during stressors such as fasting, anxiety and illnesses. This again suggests association between CVS and migraine.

Clinical Presentation

Manifestations usually begin in adolescence however they can persist into adulthood complicating care as well.

The hallmark of this disease is recurrence of nausea and vomiting cycles with complete resolution between episodes. Exam findings are nonspecific but often showed signs of dehydration such as dry mucous membranes, tachycardia, and poorly localized abdominal tenderness.

The Rome committee redefined CVS in 2016 as episodes of vomiting with at least two acute episodes over a six-month period and these episodes must occur at least one week apart but last no longer than one week.

CVS has been shown to have four phases.⁸ Beginning with the well phase in which patients are at baseline health without symptoms of nausea or vomiting. Followed by a prodromal phase lasting minutes to hours. It is characterized by nausea, fatigue, insomnia, change in temperature, diaphoresis and abdominal pain. The acute emetic phase follows with severe nausea and vomiting

persisting even after evacuation of all stomach contents. Abdominal pain is present in up to 71% of adults.¹² Many patients also experience classic migraine headache with photophobia and phonophobia. A recovery phase during which the patient returns to normal health without nausea occurs at varying lengths of time after the episode either occurring immediately in some patients while others struggle to recover over a period of hours or days.

Several physical and psychological stressors are known to precipitate episodes such as emotional events, lack of sleep, physical exhaustion, dietary triggers (e.g., caffeine intake) and menstrual cycle in women.

Diagnostic Evaluation

No specific diagnostic test exists to diagnose cyclic vomiting syndrome but rather it remains a diagnosis of exclusion. Diagnosing CVS can be challenging due to the clinical overlap with conditions. The differential diagnosis is broad and includes gastroparesis, biliary disease, Crohn's disease, intestinal pseudo-obstruction, mechanical obstruction, mitochondrial disease, eating disorder or other nervous system diseases. Due to this clinical overlap, these patients often undergo extensive negative workups with various providers over the

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(continued from page 48)

course of many years. Patients presenting during the CVS “well phase” can be burdened by multiple and exhaustive evaluations given their seemingly healthy state during physician evaluations. Workup usually includes normal imaging of the abdomen and head, blood work, gastric emptying studies and even endoscopy.

Comorbidities

Cyclic vomiting syndrome shares many similarities with neurological disease such as migraines. In fact, a personal or family history of migraines can be a leading factor in determining the diagnosis. Relationships between migraine disorders, menses, autonomic dysfunction and mitochondrial diseases are shown but not fully understood. These disorders have been established and treatments could be linked to potential therapies for CVS as well.

Migraines

Either a personal or family history of migraine has been shown to have a strong correlation with cyclic vomiting syndrome. Episodic syndromes such as functional dyspepsia, irritable bowel syndrome, or chronic/functional abdominal pain syndromes have been associated with migraine disorders. In fact, in 1922 the first associated “Abdominal Migraine” was termed in children who were observed with episodic gastrointestinal upset that later developed migraine headaches.⁹ Abdominal migraine is another disorder that shares in episodic gastrointestinal pain that is poorly localized as well as nausea and vomiting. However, this differs from cyclic vomiting in that there is less of a predominance of nausea and vomiting and more of a diagnosis that focuses on abdominal pain that persists after thorough clinical evaluation.

Mental Health Conditions

Anxiety, depression, and panic are mental health conditions that can plague patients with CVS. Anxiety is the most common mental health disorder that accompanies CVS. Studies differ in the prevalence of the disease, but some have estimated as much as 84% of those affected by CVS suffer from anxiety.^{13,14} Anxiety can be centered around anticipation of another event and exacerbated by an unclear diagnosis.

Cannabinoid Hyperemesis Syndrome

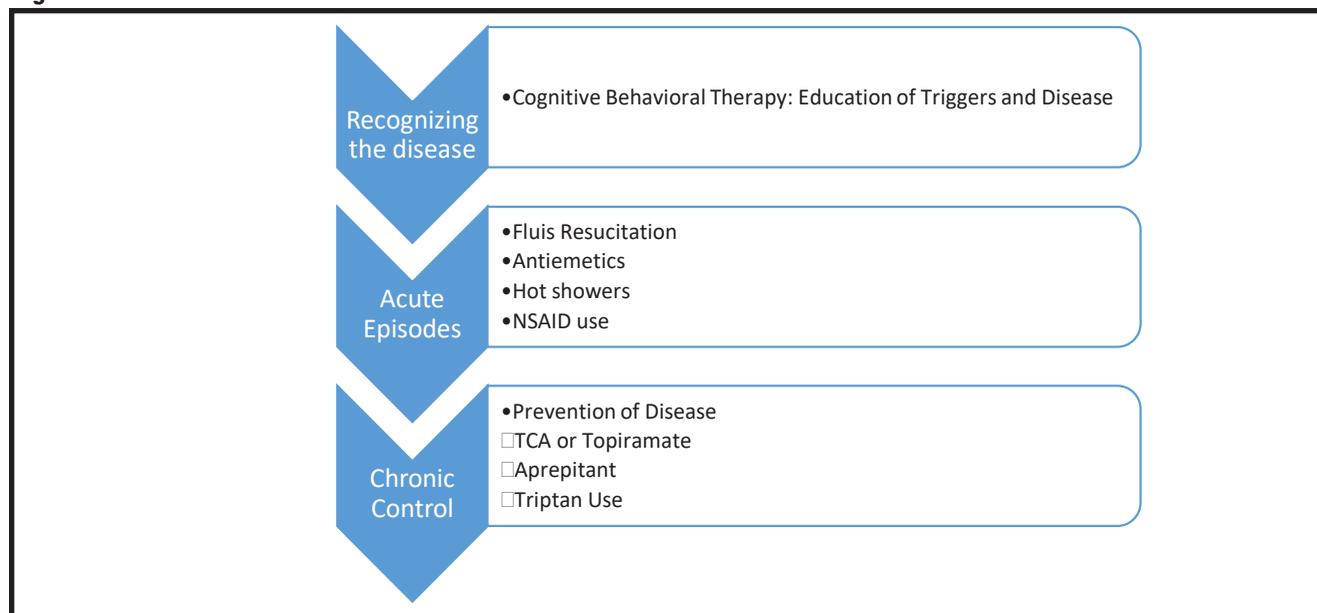
Cyclic vomiting syndrome can be mistaken with the similar symptoms seen in cannabinoid hyperemesis syndrome (CHS). Cannabis is often used for nausea, pain control, and control of seizures given its sedative effects. Legalization has increased cannabis use worldwide with the advent and steady incline in cannabis use disorders, including cannabinoid hyperemesis syndrome. In a 2015 study by emergency medicine physicians in New York, one third of patients with regular cannabis use, defined as 20 days out of a month, met the criteria for CHS.⁶

However, chemicals in cannabis such as THC have been proposed to have irritative effects on the gastrointestinal tract. A greater percentage of THC has been found in recreational cannabis and therefore hypothesized to cause a link between the two.²³ Cannabinoid hyperemesis syndrome is defined by the Rome IV criteria as chronic cannabis use followed by intractable emesis episodes similar to CVS. There is increasing overlap between cyclical vomiting syndrome as well as cannabinoid hyperemesis syndrome. However, as the name suggests, cannabinoid hyperemesis syndrome is characterized by the significant use of cannabis prior to episodes of nausea and vomiting. While cannabis may be beneficial in the nausea of cyclic vomiting syndrome, it is known to instigate an episode in cannabinoid hyperemesis syndrome.²⁴ The two differ slightly in that termination of hyperemesis syndrome in CHS is achieved with the cessation of cannabis use. Patients have also been shown to have relief with “hot bathing” with frequent hot baths or showers.⁵ The reason for this CHS relief is unclear. Interestingly, patients with CVS get similar relief with hot showers.

Treatment

Recommendations for treatment of CVS are limited given no placebo-controlled study has yet to examine any preventative or acute treatment measures. However, case studies have shown that lifestyle modification should be of prime consideration. A study in Ireland came to an interesting conclusion as well: when pediatric patients were diagnosed with CVS, the majority of patients’ utilization of medical services started to decline, thought to be a direct indication of proper

Figure 3.



diagnosis and education of disease and triggers.¹⁰ This further emphasizes the necessity of a team based approach no matter the age of the patient with both primary treatment team, emergency treatment team, and patient working together to developed a treatment plan.

Most patients report reaching for a heating pad, hot shower, or quiet place as a first line treatment in treating an attack.¹⁴ This compulsive bathing is a key treatment noted in cannabinoid hyperemesis as noted above.

CVS has been shown to be a disorder of the brain-gut axis as discussed above. Events that induce stress such as infection or menses (known as catamenial cyclic vomiting syndrome) have been shown to precipitate an event. Therefore, focusing on lowering the level of stress and identifying potential psychosocial triggers has been shown to be beneficial in patients with CVS.

Migraine and CVS Overlap

Therapy used for preventing or aborting migraines may be used for CVS given the overlap.

Migraine triggers may be involved in CVS as well, therefore avoiding them may be beneficial to patients. Foods such as alcohol, chocolate, milk, cheese, and caffeine have been shown to predispose patients to migraines and functional disorders.²¹ Avoidance of such foods may not work for everyone but should be discussed with patients

as first line therapy for the disorder.

Nonspecific treatments for migraine such as nonsteroidal anti-inflammatory drugs (NSAIDS) ironically may be useful providing symptomatic CVS relief. Nonselective beta blockers (e.g., propranolol) useful to prevent migraine headache may also have a role in preventing frequent CVS episodes. In certain countries, a combination of metoclopramide and paracetamol is used for migraines that are accompanied by nausea and vomiting. The most popular class of migraine abortive and preventative medication is known as the triptans. These are vasoconstrictors that largely replaced the ergot class as the most highly effective medications for migraines and have been shown to be effective in CVS.

Guidelines for Treatments of CVS

The American Neurogastroenterology and Motility Society and the Cyclic Vomiting Syndrome Association published guidelines outlining the distinction between mild versus moderate or severe episodes. These distinctions help further guide proposed management of disease. A moderate or severe disorder was characterized by the occurrence of equal or greater than four episodes a year, lasting over two days, with a long recovery period, as well as requiring emergency medical care or hospitalization. With this distinction, moderate or severe disease was proposed to be treated

with preventative medications such as a tricyclic antidepressant/topiramate or CoQ10. Treatment with abortive medications in acute episodes was proposed with all disease phenotypes.¹¹

Aprepitant is a substance P/neurokinin 1 receptor (NK1) antagonist. Although lacking extensive study due to its relative new emergence in 2003, aprepitant has been shown to be beneficial in chemotherapy induced nausea and post operative nausea and vomiting. Due to these advances, The American Neurogastroenterology and Motility Society and the Cyclic Vomiting Syndrome Association recommend its use as a second line prophylactic agent when tricyclic antidepressants (TCA) or topiramate has failed to show improvement in moderate to severe CVS.¹¹

In any acute episode either managed at home or with the care of medical services, adequate fluid resuscitation is of utmost importance. Additionally, antiemetics such as promethazine or zofran may be applicable based on the patient's underlying comorbidities. In small case series and retrospective trials, medications such as nasal sumatriptan, amitriptyline, riboflavin, and aprepitant (a neurokinin-1 antagonist) have been shown to have partial or complete resolution of symptoms in pediatric patients.⁹

CONCLUSION

Cyclic vomiting syndrome (CVS) has been historically underdiagnosed, leading to patient physical and psychological stress. This lack of clinical insight has led to a burden on the health care system in the US with cost estimated to be up to \$200 million annually.¹⁸ The future, however, is bright due to growing clinician CVS awareness and earlier diagnosis. Once CVS is diagnosed targeted therapy can be prescribed. In addition, new insights in the CVS risk polymorphisms cannabinoid hyperemesis syndrome overlap, and ongoing brain gut axis research may lead to new, novel therapeutic opportunities. ■

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