A 53-Year-Old Woman With Recurrent Vomiting and Migraine Headache

Clinical Scenario

A 53-year-old woman was referred to the Gastroenterology clinic after 5 admissions to the hospital for intractable nausea and vomiting during a period of 8 months. On questioning, the patient describes recurrent episodes of similar symptoms. These begin with the sudden onset of nausea. Often the nausea will be constant for days. During a matter of hours her symptoms will progress to include nonbloody emesis. Often she will vomit 4–6 times a day. Occasionally she will experience nonbloody diarrhea associated with these episodes. She can identify no triggering events or exacerbating factors, although she attributes the recent increase in her symptoms to stress from a family conflict. Warm baths seem to improve her symptoms somewhat. Typically her symptoms are preceded by an aura and migraine headache. Often her headache will resolve before the nausea and vomiting. These episodes have been occurring for about the last 1 1/2 years. She has no history of functional gastrointestinal disorders.

During the course of her multiple hospitalizations the patient was subjected to an extensive evaluation in an attempt to identify an etiology for her symptoms. A magnetic resonance imaging scan of the brain was normal. An abdominal computed tomography scan demonstrated only nonspecific abnormalities. An evaluation of her gallbladder showed a few small gallstones; a hepatobiliary iminodiacetic acid scan was normal. A gastric emptying study performed during an admission for nausea and vomiting showed normal gastric emptying time. A host of disease serologies including amylase and lipase, C1-esterase studies, celiac sprue serologies, human immunodeficiency virus testing, cardiac enzymes, and testing for paraneoplastic syndromes were negative.

No underlying etiology can be found to explain the patient’s episodic nausea and vomiting. Initially a positive toxicology for urine cannabinoids prompted consideration of cannabis hyperemesis as a potential etiology. The patient was counseled that some patients experience recurrent vomiting from cannabinoid toxicity. Her symptoms persisted after abstaining from marijuana use. Endoscopic evaluations were normal. A small-bowel follow-through was normal. Because of her persistent symptoms and the presence of a few small gallstones on ultrasound, the patient was referred to the surgery clinic for laparoscopic cholecystectomy. Unfortunately, after the operation her symptoms persisted. She was also referred to a psychiatrist, who evaluated her and diagnosed her with generalized anxiety disorder. Treatment with mirtazapine resulted in an improvement of her anxiety symptoms but did not lead to resolution of her vomiting.

The Problem

This patient’s presentation is very suggestive of cyclic vomiting syndrome (CVS) because she has recurrent episodes with symptom-free intervals and a history of migraine headache. Medical historians can trace the first descriptions of this behavior to Heberden’s Commentaries on the History and Causes of Diseases published in 1806. Almost 80 years later Samuel Gee authored On Fitfull or Recurrent Vomiting, a case series of 9 pediatric patients he treated with cyclic vomiting symptoms at St Bartholomew Hospital in London. Gee’s observations have served as the foundation for the diagnosis of CVS. Long recognized in the pediatric population, CVS has more recently been recognized as a disease that affects all ages and has recently been receiving more attention in the adult medical literature.

Cyclic vomiting in adults is characterized by a recurrent progression through stereotypical phases of illness (Figure 1). Patients begin in an interepisodic phase in which they are symptom-free. The interepisodic phase lasts weeks to months. For reasons not completely understood but often related to a stressor event, patients progress into the pre-emetic or prodromal phase. This phase is characterized by a pre-event aura. Often in this phase patients experience abdominal pain and nausea, but most are able to tolerate liquids and medications. The pre-emetic phase lasts minutes to hours. Ultimately, patients progress into the emetic phase of illness, which is characterized by persistent nausea and intractable nausea and vomiting. In this phase patients often become dehydrated and present for hospital admission. This phase lasts hours to days. Finally, patients progress into the recovery phase in which vomiting slows, and they are able to tolerate oral intake.

The Rome III working teams on functional disorders published diagnostic criteria for CVS in adults in 2006. A diagnosis of cyclic vomiting required fulfillment of 3 criteria for the last 3 months with onset of symptoms at least 6 months prior: (1) stereotypical episodes of vomiting regarding onset (acute) and duration (less than 1 week), (2) three or more discrete episodes in the prior year, and (3) absence of nausea and vomiting between episodes.

Further supportive criteria include personal or family history of migraine headaches.

Some authors have proposed subtypes of adult CVS to include those with migraines, those with hypertension during

Abbreviation used in this paper: CVS, cyclic vomiting syndrome.
Pathophysiology

Several case series describing CVS in adult patients have identified a number of similarities in the patient population. Migraine headache is common in patients with CVS, with a prevalence reported from 24%–70%. Often control of migraine symptoms leads to improvement in CVS attacks. Severe abdominal pain is common during the emetic phase in adults and was reported in 58%–71% of patients. This has important implications because often patients with CVS seek care in emergency departments and can be perceived as drug seekers. Many CVS patients can identify a stress or event that precipitates attacks. Some patients will notice that episodes are triggered by certain foods; chocolate, cheese, and monosodium glutamate are sometimes implicated. Frequent, patients with CVS are suspected of having other chronic medical problems. One study found that 5% of patients referred to a tertiary care center for gastrointestinal were diagnosed with CVS. In another report 39% of patients with undiagnosed CVS had surgery for their symptoms with no improvement. Finally, adult patients with CVS frequently have psychiatric disorders including anxiety, depression, and panic disorder. The combination of these factors makes the CVS patient population a suspicious and often difficult population to care for.

A variety of hypotheses exist regarding the etiology of cyclic vomiting. Clinical observations, however, have generated research into a host of potential etiologies including hormonal dysfunction, autonomic dysregulation, motility disorders, food allergy, mitochondrial DNA disorders, and chronic cannabis use.

In the pediatric literature it has been reported that up to 70% of CVS is precipitated by a stressor. One proposed mechanism is stress release of corticotropin-releasing hormone, which precipitates a cascade of endocrine events ultimately affecting sympathetic tone in specific regions of the brain as well as altering vagus-mediated gastric motor activity. Other research has explored the link between catecholamine and prostaglandin activity and recurrent spells of vomiting in children.

A link between autonomic dysregulation and cyclic vomiting has been objectively demonstrated in adults as well as in children with migraine headache as well as cyclic vomiting. Positron emission tomography scans of patients with CVS have also demonstrated abnormalities similar to those seen in patients with migraine. Autonomic dysfunction is not a requirement for diagnosis of adult CVS, however.

It has been demonstrated in multiple studies that alterations in baseline gastric motility are present in CVS patients during all phases of the illness. It is unclear whether this is the cause of CVS or some consequence of the illness.

A number of other clinical observations have prompted investigation of other potential mechanisms of pathogenesis. Suspecting a relationship between mitochondrial enyzmopathies and CVS, some have proposed that an inability to meet the energy demands of stress might account for the autonomic dysregulation present in CVS. Others have suggested that elimination of allergens established by skin testing improved symptoms of CVS in children, although this hypothesis has not been tested in adults.

Finally, it has been suggested that chronic cannabis use results in a cannabis toxicity that ultimately causes CVS symptoms.

Management Strategies and Supporting Evidence

There are no evidence-based strategies for management of CVS. In general, the goal of treatment is to prevent patients from entering the emetic phase of illness or to relapse into the emetic phase of the illness. Quality empiric guidelines have been developed by experts on the basis of their experience with CVS and are available on the Internet.

Patients without symptoms between exacerbations should receive medications for migraine prophylaxis such as propranolol, tricyclic antidepressants, or antiepileptic medications that have been shown to be useful in migraine, like zonisamide (Zonegran) or levetiracetam (Keppra), which have been shown to be useful in uncontrolled trials. When patients begin to have aura or prodromal symptoms, efforts should focus on preventing progression to the emesis phase. These efforts should include antiemetics, abortive migraine medications (triptans), pain medications, and benzodiazepines. Simple interventions like lying down in a dark, quiet place might also be useful. These efforts should continue if the attack progresses into the emetic phase, but IV fluids should be added, and consideration

Figure 1. Algorithm for management of CVS. Adapted from Fleisher DR, Gornowicz B, Adams K, et al. Cyclic vomiting syndrome in 41 adults: the illness, the patients, and problems of management. BMC Med 2005;3:20.
might be given to adding acid-suppressive medications like H₂ blockers or proton pump inhibitors.

Identifying triggers and exacerbating stressors remains fundamental in CVS, as in any illness. Careful history taking, dialogue, and collaboration with the patient and their family members are critical to successful management and avoidance of hospitalizations.

Areas of Uncertainty
Much remains unknown about CVS. It is clear that there is some relationship between CVS, classic migraine, and abdominal migraine. What is unclear is whether these are spectrums of the same disease or different diseases entirely. There are no randomized clinical trials of treatment in CVS. Finally, the relationship between marijuana and CVS remains somewhat controversial; clearly some patients with CVS will use marijuana in an attempt to control their symptoms. It is also apparent that some marijuana smokers will develop cyclic, recurrent vomiting that resolves with marijuana abstinence. Clinicians need to carefully and tactfully approach the issue of marijuana use with their patients. Some patients might require supervised detoxification with a tapering dose of a pharmaceutical cannabinoid; however, this remains controversial.

Published Guidelines
Two recent publications have dealt extensively with CVS in adults and are included on our suggested reading list. Although developed primarily for the pediatric population, Dr David Fleisher’s web site has an excellent empiric guide to management of CVS.

Recommendations
In this patient, we advocated strict marijuana abstinence because it was unclear from her initial presentation whether her marijuana use started before or after her vomiting episodes began. Because her vomiting and headaches persisted after abstaining, it was clear that her vomiting was not from cannabinoid hyperemesis syndrome. At this point, her migraine medications were adjusted; we increased her dose of zonisamide (Zonegran), and her vomiting episodes abated. She was symptom-free at 6-month follow-up, with no additional hospitalizations for vomiting.

Suggested Reading

Reprint requests
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Conflicts of interest
The authors disclose the following: Dr Winstead serves as a consultant for UCB. Dr Nass discloses no conflicts.