Clinical Vignette

Adult Cyclic Vomiting Syndrome Successfully Treated with Intranasal Sumatriptan

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Cyclic vomiting syndrome is an increasingly recognized cause of nausea and vomiting in adults. We report the case of a 47-year-old man with recurrent episodes of intractable nausea and vomiting for one year. His symptoms persisted for 4–7 days and then resolved spontaneously, only to return after periods of time ranging from one week up to a month. After an extensive workup, which failed to determine any causative explanation for his symptoms, he was diagnosed with cyclic vomiting syndrome. His episodes of vomiting were successfully terminated with the use of intranasal sumatriptan. In this case, we highlight that sumatriptan effectively aborted symptoms in an adult patient with cyclic vomiting syndrome. Increasing physicians' awareness of adult cyclic vomiting syndrome may improve care of patients suffering from this debilitating condition.

KEY WORDS: adult cyclic vomiting syndrome; treatment; sumatriptan; triptan.
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INTRODUCTION

Cyclic vomiting syndrome is a well-documented cause of chronic nausea and vomiting in children. However, it also occurs in adults and often goes undiagnosed for years due to a general lack of knowledge and understanding of the condition among physicians[1–3]. Treatment of patients depends on the frequency and severity of the vomiting episodes and may include the following: 1) prophylactic medications and 2) medications to help abort an episode[4,5]. Based on small case series, experts recommend sumatriptan during early stages of vomiting in children with cyclic vomiting syndrome[6]. Currently there are no studies of sumatriptan in adults with cyclic vomiting syndrome and recent review articles present conflicting recommendations regarding the use of sumatriptan in adults with cyclic vomiting syndrome[2,3,7]. The following are the objectives of this article: 1) Present a case report of sumatriptan effectively aborting symptoms of adult cyclic vomiting syndrome without migraine diathesis or family history of migraine. 2) Educate the internist to recognize cyclic vomiting syndrome as an infrequent, but known cause of nausea and vomiting in adults. 3) Discuss pathogenesis, diagnosis, and treatment of adult cyclic vomiting syndrome.

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CASE REPORT

A 47-year-old African–American man presented with intermittent episodes of vomiting for the past year. When the symptoms first appeared, he would only feel nausea that would appear suddenly and might even wake him from sleep. The symptoms gradually progressed over the subsequent several months, and he began to vomit as well. For the past three to four months before presentation, the symptoms had assumed a predictable pattern and were now reliably associated with a prodrome of mid-epigastric abdominal discomfort that lasted less than 24 hours. This would lead into the acute onset of recurrent vomiting, usually beginning in the early morning hours. Up to 30 episodes of vomiting occurred per day, and were often associated with severe, diffuse abdominal pain and an urge to defecate, though a bowel movement would not relieve his symptoms. Vomiting would continue for 4–7 days, often requiring hospitalization for IV hydration, and then would end abruptly. A symptom-free period would then ensue, lasting from one week to a month, after which the symptoms would return exactly as before. There were no clear precipitating factors for these episodes, and the vomiting was exacerbated by drinking water and eating large meals. Efforts to modify his diet in order to identify any foods which might be exacerbating his condition were unsuccessful.

The patient's past medical and surgical history was significant for hypertension, gastroesophageal reflux disease and was status-post cholecystectomy, reportedly for acute cholecystitis, 20 years prior. He had lost over 50 pounds since the onset of his symptoms a year ago but denied fevers, sick contacts, headaches, vision changes, numbness, or blood in his stool or emesis. He stated that he was dizzy after vomiting but otherwise denied vertigo or lightheadedness. Though frustrated by the repeated hospitalizations for his condition, the patient was never clinically depressed or overly anxious. Medications included hydrochlorothiazide and lansoprazole. He was unmarried and worked as a plumber. He smoked one pack of cigarettes per day for 20 years and denied alcohol or illicit substance abuse. Family history was significant for coronary artery disease and hypertension and negative for migraine headaches or gastrointestinal disorders.

Physical examination at initial presentation was significant for temperature 98.8 Fahrenheit, pulse 90 regular sitting and 94 standing, blood pressure 122/78 sitting and 120/70 stand-

ing, respiratory rate17, and weight 147 pounds (originally 200 pounds one year prior, by report). Lungs were clear and heart sounds were normal. The abdomen was soft, non-tender, non-distended, with normal bowel sounds and no hepatosplenomegaly, with a well healed surgical scar in the right upper quadrant. Neurologic examination was normal.

Laboratory evaluation revealed normal serum electrolytes, serum creatinine 1.1 mg/dL [normal range: 0.8–1.3 mg/dL], blood urea nitrogen 21 mg/dL [10–20 mg/dL], white blood cell 8.2 THO/uL [4.0–11.0 THO/uL] (82% segmented neutrophils, 14% lymphocytes, 4% monocytes), hemoglobin 15.7 g/dL [13.5–17.5 g/dL], alanine aminotransferase 26 U/L [21–72 U/L], aspartate aminotransferase 16 U/L [17–59 U/L], total serum bilirubin 0.7 mg/dL [0.0–1.2 mg/dL] , amylase 70 U/L [0–140 U/L], lipase 48 U/L [0–300 U/L], albumin 2.9 g/dL [3.5–5.8 g/dL], pre-albumin 23.0 mg/dL [16.6–43.1 mg/dL], normal urinalysis, HIV negative, negative urine toxicology testing, TSH 1.0 uIU/mL [0.4–4.0 uIU/mL] and ESR 4 mm/h [0–15 mm/h].

An extensive workup was initiated over the next several months including abdominal radiography, ultrasound, CT/MRA/MRI of the abdomen, MRI of the brain, upper GI with small bowel follow-through and upper and lower endoscopy, all of which failed to reveal any abnormality to explain his symptoms. These studies were each performed while the patient was symptomatic during his multiple hospitalizations over several months. A gastric emptying scan was performed while the patient was asymptomatic and off any prokinetic agents. It demonstrated accelerated gastric emptying with 65% of contents removed by 30 min, 73% removed by 60 min, and 87% removed by 92 min.

Trials of anti-emetics, nutritional supplementation, tricyclic antidepressants, histamine-receptor blockers, proton pump inhibitors and prokinetics all failed to reduce or resolve the patient's symptoms. Ultimately, a trial of sumatriptan intranasal 20 mg in one nostril, given during the prodromal phase, successfully prophylaxed against the emetic phase of the illness. After one year of follow-up, although he continued to sense prodromal symptoms, each was successfully aborted with the use of sumatriptan and he has not required hospitalization since.

DISCUSSION

Cyclic vomiting syndrome is characterized by recurrent periods of intense nausea and vomiting lasting hours to days, with symptom-free periods between episodes lasting weeks to months[8]. The symptoms of cyclic vomiting syndrome may interfere with physical functioning, education, employment and personal relationships and can have a significant impact on a patient's overall quality of life[9]. It often goes undiagnosed for years in adults, with reports suggesting a lag in diagnosis for up to 8 to 21 years from onset of symptoms[2]. While the disorder in children and adults likely represents a continuum, there are some differences in presentation; adult patients have a longer delay to diagnosis, episodes are longer in duration, and they are more likely to have inter-episodic nausea and dyspepsia[2]. Although the patient history can be very suggestive of cyclic vomiting syndrome, it is a diagnosis of exclusion and must be supported by negative laboratory, radiographic, and endoscopic testing[6]. Patients often undergo multiple diagnostic procedures, some of which may be invasive in nature. In a study of 41 undiagnosed adult patients with cyclic vomiting syndrome, 39% underwent one or more surgical procedures as part of their diagnostic evaluation[1].

Phases

Cyclic vomiting syndrome can be divided into four phases: interepisodic, prodromal, emetic and recovery[1–3]. The interepisodic phase occurs between episodes when the patient is relatively symptom free and typically lasts weeks to months. The prodromal phase occurs when the patient begins to sense the approach of an episode, principally symptoms of nausea, sweating, abdominal pain, heat or cold intolerance, urge to defecate, food aversion, irritability, or panic. This usually lasts minutes to hours[2,3]. Potential triggers of acute episodes include infection, psychological stress, motion sickness, sleep deprivation, physical exhaustion, menses, and certain foods (chocolate, cheese, red wine, monosodium glutamate)[2]. The emetic phase is characterized by intense nausea, vomiting, abdominal pain, and lethargy lasting from hours to days. The recovery phase begins with lessening of nausea, followed by hunger, and tolerance of oral intake[1–3].

Pathogenesis

Cyclic vomiting syndrome may involve dysregulation of neuroendocrine pathways responsible for control of nausea and vomiting. One model suggests that triggers, such as psychological or infectious stress, up-regulate vomiting response in genetically inclined patients. The predisposing factors for this include personal or family history of migraines, hypothalamic-pituitary-adrenal axis defects, gastric dysrhythmias, food allergies, and energy deficits due to mitochondrial dysfunction[2].

Diagnosis

The Rome III Criteria for diagnosis of cyclic vomiting syndrome were published based on the consensus opinion of an international panel of clinical investigators in 2006 (Table 1)[8]. Initial laboratory testing should include complete blood count with differential, basic metabolic profile, liver function testing, amylase, lipase, urinalysis and pregnancy testing if applicable. Abdominal radiographs should be performed to rule out gastrointestinal obstruction. Differential diagnosis of cyclic vomiting syndrome (Table 2) is very broad and further testing should be tailored to the individual patient clinical history and exam[2]. As a diagnosis of exclusion, most testing in cyclic vomiting patients will be negative and initial therapeutic trials could preclude

Table 1. Rome III Diagnostic Criteria for Cyclic Vomiting Syndrome

Must include all of the following criteria fulfilled for the last three months with symptom onset at least 6 months before diagnosis:	
1.	Stereotypical episodes of vomiting regarding onset (acute) and duration (less then 1 week)
2.	Three or more discrete episodes in the prior year
3.	Absence of nausea and vomiting between episodes in the prior year
Supportive criterion: history or family history of migraine headaches.	

Source: Ref. [8].

Table 2. Disorders That Mimic Cyclic Vomiting Syndrome in Adults

Gastrointestinal disorders	Typical evaluation
Gastric disorders	
Peptic ulcer disease	Upper endoscopy
Gastroparesis	Gastric emptying scan
Gallbladder disorders	
Cholecystitis	Abdominal ultrasound
Biliary tract dysmotility	HIDA scintigraphic imaging
Small bowel disorders	
Intermittent small bowel obstruction	CT enterography
Chronic intestinal pseudo-obstruction	Abdominal obstruction radiographic series
Malrotation with volvulus	Upper GI with small bowel follow-through
Other	
Abdominal migraine	Similar to CVS
Extra-intestinal disorders	
Central nervous system abnormalities	
Mass	Head MRI
Hydrocephalus	Head MRI
Renal Disorders	
Nephrolithiasis	Urinalysis
Ureteropelvic junction obstruction	Renal ultrasound
Hormonal and metabolic disorders	
Adrenocorticoid insufficiency	Plasma cortisol
Acute intermittent porphyria	Urinary porphyrins
Other	
Chronic cannabis use	Response to cessation of cannabis use
Psychogenic vomiting	Psychiatric evaluation

Source: Adapted from Ref [2]

further testing. One study in children determined that an upper GI with small bowel follow-through plus empiric treatment with antimigraine medications was the most cost-effective initial diagnostic[10]. In the patient reported here, gastroparesis was entertained as a diagnosis with his frequent vomiting episodes. Interestingly, a gastric emptying test showed rapid rather than delayed gastric emptying. Cyclic vomiting syndrome has been shown to be associated with rapid early gastric emptying during asymptomatic periods. In a study of 31 patients with cyclic vomiting syndrome, Namin et al. found that 77% of patients had rapid gastric emptying [18].

Treatment

Because of the lack of controlled treatment trials in adult patients, treatment recommendations are largely adapted from evidence in pediatric population or are derived from open label trials reported in case series[2,3,11]. A multidisciplinary approach, involving experienced gastroenterologist, primary care physician, nursing support, as well as a psychiatrist or psychologist has been shown to be successful in children and is recommended in adults[2,12].

Specific management recommendations are based on the individual phase of the cyclic vomiting cycle[11]. The goal during the interepisodic phase is to prevent episodes by avoidance of triggers and prophylactic treatment. Patients with frequent, long, or difficult to abort episodes may benefit from prophylactic treatment[2,3,11]. Tricyclic antidepressants (TCA) have been shown to be effective in treatment of cyclic vomiting syndrome with amitriptyline recommended in a step-up approach for treatment of adults with cyclic vomiting syndrome[9]. If amitriptyline cannot be tolerated, TCAs with fewer side effects can be initiated[2]. Prophylactic antimigrane medications such as propranolol can be considered, especially in patients with a personal or family history of migraines[1–3]. In patients with nausea, ondansetron, promethazine, or prochlorperazine have been helpful. Abdominal pain that persists after the acute attack may require tramadol or other non-narcotic analgesics. In some patients narcotic use may be necessary[2].

The objective of treatment during the prodromal phase is to abort the onset of vomiting when the patient begins to sense nausea. Antiemetic agents, especially ondansetron, promethazine, and diphenhydramine have shown to be clinically beneficial[2,3]. Anxiolytics (lorazepam, or alprazolam), and pain medications (ibuprofen, tramadol, dilaudid, oxycodone) may be required to help induce sleep and control abdominal pain[1,2,6,11].

The goal of treatment of emetic phase is to terminate the episode as soon as possible and to address consequences and possible complications of vomiting. Dehydration is common and should be corrected with intravenous fluids. As fluid resuscitation is initiated, the episode can be aborted with ondansetron and lorazepam[2,3]. Opiates may be necessary to control pain. If the episode cannot be terminated, sedation (with chlorpromazine in combination with diphenhydramine) may be necessary to relieve the patient's distress[1–3,11].

Recovery depends on each individual and the adequacy of treatment during the emetic phase. Prophylactic medication should be resumed as soon as possible[2,3,11]. The patient's emotional well being strongly influences the success of management. Many adults with cyclic vomiting syndrome experience episodes triggered by panic and patients may become anxious and fearful of future attacks. Feelings of optimism and gaining control are, therefore, of great importance in management of cyclic vomiting syndrome[13].

Migraine/Sumatriptan

Cyclic vomiting episodes resemble a migraine and many children with cyclic vomiting syndrome progress to develop migraine headaches in adulthood. Experts believe that a continuum may exist between cyclic vomiting, abdominal migraine and migraine headaches[3,14]. Similarities in the mitochondrial DNA of patients with cyclic vomiting syndrome and patients with migraine without aura have also been found[15]. Abdominal migraine is a functional gastrointestinal disorder affecting children and adolescents, and less commonly adults, characterized by recurrent episodes of typical abdominal pain, with symptom free intervals. In children, this may be difficult to distinguish from cyclic vomiting syndrome, as there is often a significant overlap in symptomatology with both syndromes. In abdominal migraine, though the predominant symptom is abdominal pain; whereas in cyclic vomiting, the predominant symptom is the vomiting[16]. Patients with high frequency and greater severity of symptoms may benefit from prophylaxis with antimigraine medications, such as TCA, cyproheptadine, and propranolol[4,5].

Sumatriptan is a $5HT_{1D1B}$ agonist, FDA approved for acute treatment of migraine headaches in adults. Based on a small case series, experts recommend sumatriptan in children with cyclic vomiting syndrome during the early stage of vomiting[6]. Among the few reports of sumatriptan use in adult cyclic vomiting patients, most involve patients with a concomitant personal of family history of migraine headaches. Benson et al. reported on a 19-year-old male who was successfully treated

during the emetic phase with subcutaneous sumatriptan and was discharged within 40 hours of admission[17]. More recently, Pareek et al. stated that sumatriptan can be used to treat migraine headache during a cyclic vomiting episode, but recommend against its use to prevent vomiting secondary to "little evidence to its efficacy in ameliorating gastrointestinal symptoms during prodromal or vomiting phases"[3]. Olden et al. suggest that sumatriptan administered intranasally or subcutaneously can be efficacious in cyclic vomiting syndrome patients who have a personal or family history of migraine[7]. Lastly, Abell et al. propose sumatriptan as an option during emetic phase, but caution that "the use of this class of antimigrane drugs is less well studied in adult patients"[2]. Our case demonstrates that intranasal sumatriptan effectively aborted symptoms in an adult with cyclic vomiting syndrome without migraine diathesis or family history of migraine.

SUMMARY

Adult cyclic vomiting syndrome is defined as three or more periods of intense nausea and vomiting lasting hours to days, with a return to usual health between episodes. In adults it may occur more often than previously thought and is postulated to be the cause of multiple hospital and emergency department visits. The treatment of cyclic vomiting syndrome may include antimigrane prophylaxis, antiemetics, analgesics, anxiolytics, IV fluids, opiates and sedatives. Studies in children support the use of 5HT receptor agonists, such as sumatriptan, during the prodromal phase of cyclic vomiting syndrome. While additional studies are necessary to fully support the use of sumatriptan in adults, its use should be considered, especially in patients with personal or family history of migraines. As in our case, their use may successfully abort a full constellation of debilitating symptoms from occurring and can greatly improve the patient's overall quality of life.

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